BERNHARD NOCHT INSTITUTE FOR TROPICAL MEDICINE

BERNHARD-NOCHT-INSTITUT FÜR TROPENMEDIZIN

BERNHARD-NOCHT-INSTITUT
FÜR TROPENMEDIZIN

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Foto: M. Jacobs/P. Kämpfer, BNI.

Ansicht der im Bau befindlichen Laborerweiterung vor dem historischen Institutsgebäude von 1916.
View of the laboratory extension in front of the historic institute building (dating from 1916).

Management / Leitung

The Bernhard Nocht Institute for Tropical Medicine is member of the Leibniz Association and an institution of the
Free and Hanseatic City of Hamburg
Ministry of Science and Health

Das Bernhard-Nocht-Institut für Tropenmedizin (BNI) ist ein Mitglied der Leibniz-Gemeinschaft und eine Dienststelle der
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The Bernhard Nocht Institute for Tropical Medicine is financed jointly by the Federal Government and the States of the Federal Republic of Germany.

Das Bernhard-Nocht-Institut für Tropenmedizin wird nach §91 b Grundgesetz gemeinsam von Bund und Ländern finanziert.

	2004	2005
Total research budget / Gesamthaushalt	13,95 Mio EUR	14,33 Mio EUR
funding by Federal governmental bodies (excl. investments) *davon institutionelle Förderung durch Bund und Länder (exkl. Investitionen)*	9,44 Mio EUR	9,19 Mio EUR
third party funding by EU, foundations, DFG etc. *davon Drittmittel von EU, Stiftungen, Deutsche Forschungsgemeinschaft etc. (ohne durchlaufende Gelder)*	3,05 Mio EUR	3,44 Mio EUR

Third party funding / Drittmittel

Additional financial support was granted by the following organizations:
Weitere Mittel erhielt das Institut von folgenden Organisationen:

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Introduction

This reporting period started with a suspected case of avian influenza infection admitted to the Bernhard Nocht Institute (BNI) which led to greatest excitement in the media. The diagnostic laboratory of the BNI gave the all-clear within a few hours, however, a slump in the market had already occurred in this time. Again an emerging infectious disease had suddenly come to the attention of the public and again the BNI had been proven to be a centre of competence for infectious diseases. However this reputation did not suffice to acquire enough patients for the Clinical Department to overcome the economic pressures in the public health system. It became clear in 2005 that the Clinical Department could only survive by fusion with a large hospital. Thus, at the end of this reporting period with the close of 2005 the Clinical Department had to be sold to the University Medical Centre Hamburg-Eppendorf (UKE). After more than 100 years the in-patient medical care of patients with tropical infections is now no longer present in the BNI building. Other remarkable events were the start of the constructions of the extension building, the conclusion of a cooperation agreement with the German Armed Forces Medical Service and the award of multiple honours for members of the BNI.

The Bernhard Nocht Institute

Since its inception on 1st October 1900 as *Institute for Maritime and Tropical Diseases* the BNI has been Germany's largest research institute for tropical medicine and combines laboratory research with clinical studies and patient care. The BNI is a government institution affiliated to the Federal Ministry of Health and the Ministry of Health of the State of Hamburg and is financed jointly by the Federal Government and the States of the Federal Republic of Germany. It is a member of the Leibniz Association that comprises institutes of national importance. The BNI has 280 members (including diploma students and guests working for short time periods), 40 staff scientist positions and employs altogether 90 scientists including scientists paid from grants and PhD students.

Mission of the BNI

As the German centre for research in tropical medicine the Bernhard Nocht Institute is dedicated to research, training and medical care in the area of human infectious diseases which are of particular relevance in the tropics. It is the primary mission of the BNI to develop means for the control of these diseases. Secondary missions are to provide expertise for regional and national authorities and to (directly and indirectly) improve health care for national and regional citizens in regard to diseases of the tropics.

The Central Diagnostic Unit performs specialized diagnostic tests for the detection of tropical viruses and pathogens causing parasitic diseases. The unit serves as the National Reference Centre for Tropical Infections for Germany. For work with haemorrhagic fever viruses a biosafety level (BSL) 4 laboratory is operated. Until the end of 2005, a clinical department with 62 beds and an out-patient clinic for patients with tropical infections was an integral part of the BNI. The hospital and its staff were entirely financed by the revenues from health insurances. For economic reasons the ownership of the hospital was transferred to the University Medical Centre Hamburg-Eppendorf (UKE).

The BNI has multiple educational activities. It is active in postgraduate training in the area of tropical medicine, parasitology, immunology and molecular biology. In the reporting period 51 diploma and doctoral theses were completed. Presently, thirteen members of the BNI are teaching at the University of Hamburg at the Faculties of Medicine, Biology and Chemistry. Three members of the institute hold full professorships (for Molecular Parasitology, Immunology and Molecular Tropical Medicine) at the University of Hamburg. A three-month's course on tropical medicine is held each year that is approved as an officially accredited diploma course by the German Medical Board and the American Society of Tropical Medicine and Hygiene.

Research

The Institute conducts disease-oriented basic research and applies state-of-the-art techniques in cellular biology, molecular genetics and immunology to the characterization of host-pathogen-interactions in tropical infectious diseases. The research activities of the BNI concentrate on three areas:

(1) cellular and molecular biology of infectious agents that cause tropical diseases,
(2) the host response to those agents and its role in protection and pathology, and
(3) a disease oriented approach to pathogenesis and pathology.

Accordingly, the studies focus on infectious diseases caused by parasites and tropical viruses. Main topics of work are pathogenicity factors and cell biology of parasites, the analysis of the host-parasite-interaction including immunological defence mechanisms, and the definition of genes causing susceptibility to certain tropical infections. In all these ventures, special emphasis is put on two issues: relevance for disease, prevention and control, and use of tropical infections as models for general issues in medicine and biology.

Organization

To fulfil these aims the BNI has a specific organizational structure. Three scientific sections (Parasitology, Medical Microbiology, Tropical Medicine) contain departments established for longer periods of time and

temporary research groups. These groups are usually installed for a limited period of time only and will be replaced by new groups according to scientific necessity.

The *Parasitology Section* contains the Departments of Molecular and Biochemical Parasitology as well as several research groups working on pathogenicity factors, biology of pathogens including biochemical pathways and mechanisms of adaptation and evasion. The *Medical Microbiology Section* contains the Department of Immunology working on host-responses to parasites, the Department of Virology, concentrating mostly on tropical viruses, the Department of Helmintholo-gy, a Central Diagnostic Unit acting as National Reference Centre for Tropical Infections and the animal experimentation facilities. The *Tropical Medicine Section* contains the Departments of Molecular Medicine, mainly concerned with the elucidation of host determinants of pathogenesis and clinical outcome, the Department of Pathology, an international reference laboratory for AIDS pathology, the Research Group Infection Epidemiology, the Kumasi Centre for Collaborative Research in Tropical Medicine in Kumasi, Ghana and, from 2006, a clinical research group headed by Prof. Gerd-Dieter Burchard, chief physician of the former Clinical Department. The close linkage with the *Clinical Department* has provided a distinctive advantage to the BNI. It is a valuable addition to clinical research performed in the tropics because patients seen in Hamburg usually have primary infections with only one infecting agent, and intensive and long-term studies applying high technology are possible in Hamburg.

Major areas of research

In its research work the BNI concentrates on selected important tropical infections, due to its limited resources. These infections are addressed in a multidisciplinary way by institute-wide collaborations, a prominent feature of the scientific work at the BNI. Most scientific work directly or indirectly leads to projects participating in one of these areas. In all these studies the BNI aims to span the research from the bench to the field, i.e. from the molecular details to studies in the tropics. During the reported time period these were malaria, amoebiasis and filariasis. Other major topics of research were viral haemorrhagic fevers, HIV/AIDS and leishmaniasis.

Malaria research is the largest research area with institute-wide co-operations ranging from the characterization of plasmodial molecules to clinical studies about treatment of malaria in Ghanaian children. Projects at the Department of Parasite Biochemistry characterize key enzymes of the glutathione metabolism and polyamine synthesis of *Plasmodium falciparum* at the molecular level for a possible exploitation for chemotherapy. The complete life cycle of *P. berghei* is available and allows access to sporozoites and liver stages. Down-regulation of apoptosis of infected hepatocytes by sporozoites during the hepatic phase is studied as well as the immune response to liver stages. Work is also performed on the identification of molecules involved in cell invasion and on mechanisms of sorting and trafficking of parasite molecules in infected erythrocytes. Studies in Ghana are concerned with the identification genes involved in susceptibility for or resistance to severe malaria by a genome-wide linkage analysis within the German National Genome Network and with the effect of intermittent treatment with sulfadoxine-pyromethamine for malaria control within the German Malaria Initiative.

Amoebiasis research was established as the first institute-wide research programme in 1988, covering a variety of aspects concerning the biology and pathogenicity of *Entamoeba histolytica*. In 1989, the group of Egbert Tannich had first described that pathogenic and apathogenic amoeba can be distinguished by molecular genetic methods, a finding that had enormous impact on diagnosis and therapy of the disease. The work in the last years concerned the analysis of molecules involved in pathogenicity, the genome organization of *Entamoeba* including the genetic comparison between *E. histolytica* and *E. dispar,* the epidemiology of the infection (a collaborative project with the Faculty of Medicine of the University of Hué, Vietnam) and clinical studies on treatment strategies. A candidate for a vaccine has been identified, a peptide of the large 170 kD galactose specific surface lectin, that leads to protection in experimental infection of animals.

Filariasis research has a long history at the BNI having started already in the 1960ies. The main topic was onchocerciasis (river blindness) caused by the filaria *Onchocerca volvulus* but work on lymphatic filariasis is also performed. Again the studies reach from the molecular tailoring of antifilarial compounds to patient-related studies in the tropics. Proteases of filaria are cloned and characterized which allow the developing worm and the microfilariae the migration through the skin and biochemical pathways exploitable for the design of new antifilarial drugs are studied. BNI scientists were able to identify endosymbiotic *Rickettsia*-like bacteria of the genus *Wolbachia* present in most filarial species as a new target for chemotherapy in animal experiments and subsequently in clinical studies in Ghana. These *Wolbachia* are not only essential symbionts for the filariae but also play a role in the pathology since *Wolbachia* surface proteins are a major stimulant for the innate immune system. Immunological effector mechanisms were analysed and genetic differences underlying the various manifestations of the infection are identified in a genome-wide linkage analysis to identify host genes relevant to protection.

Research on **haemorrhagic fever viruses** is another major topic at the BNI. Work addresses the genetics of Lassa virus, the pathogenesis of Lassa hemorrhagic

fever and the epidemiology of such viruses in different African countries. New diagnostic methods for haemorrhagic virus infection were established and used in epidemiological studies and in the Central Diagnostic Unit. The Department of Virology is a WHO Collaborating Centre for Arboviruses and Haemorrhagic Fever Viruses and received patient specimens from several European countries and from outside of Europe. The new head of the department PD Dr. Stephan Guenther coordinates a European network of BSL 4 laboratories which develops standardized PCR-assays for detection of hemorrhagic fever viruses and variola virus. Dr. Christian Drosten, head of the recently established Research Group Clinical Virology, coordinates a EU consortium on Genomic inventory, forensic markers and assessment of potential therapeutic and vaccine targets for viruses relevant in biological crime and terrorism.

Research on the Kinetoplastidae **Leishmania and Trypanosoma** is performed in joint projects of several laboratories. The regulation of conversion of *Leishmania* from the insect stage to the amastigote form in the mammalian host, signal transduction mechanisms essential for infectivity and the genetics of resistance to chemotherapy are investigated. The role of various effector cells in the immune defence against leishmania and trypanosomes including components of the innate immune system are also addressed.

AIDS research has a long history at the BNI since the first patients with the hitherto unknown infection were treated in the early 1980ies. The distribution of HIV is studied in the lymphoid tissue of patients and the role of glycosylation for the antibody response to major neutralizing epitopes of HIV is characterized. A European Union consortium for research on novel techniques to vaccinate against HIV is led by Prof. Racz, head of the Department of Pathology.

Collaborative research in the tropics

The BNI has many collaborations with institutions in developing countries and several of these have led to longstanding partnerships. Most prominent is the *Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR)*, which was founded in 1997 and established a partnership with the School of Medical Sciences, Kwame Nkrumah University of Science and Technology in Kumasi, Ghana. The cooperative centre was set up according to a state agreement between the Republic of Ghana and the City State of Hamburg, to foster longstanding contacts to scientists of the host country. Its hallmark is each research project being carried out jointly by scientists from Hamburg and Kumasi. A major goal of the KCCR is capacity building, to recruit young Ghanaian graduates for scientific research.

Due to a larger number of projects financed by grants the KCCR has meanwhile grown to more than 40 staff employees and in addition many temporary workers, most of them working in projects and paid by grant money. The KCCR does not perform research itself but serves as a platform and infrastructure for the acquisition and performance of research projects. Since 2 years it disposes of research campus. Its construction and equipment were financed half by grants (from the Volkswagen Foundation and a donation from the *Vereinigung der Freunde des Tropeninstituts Hamburg*), and half by the Senate of Hamburg and the Ministry of Health of the Federal Republic of Germany. Peripheral laboratories are maintained in Agogo, Dunkwa and Essiama. It is our hope that the KCCR will develop into an international research platform attractive to scientists of other institutions who are invited to perform research here.

Other longterm co-operations under official agreements are fostered with the University of Hué Medical School (Vietnam), the Central Institute of Drug Research, Lucknow (India), and the Uganda Virus Research Institute in Entebbe.

Developments in 2004 and 2005

A chronicle of important events during the period of this report is given in the appendix.

Clinical Department

A major change for the BNI was the transfer of its Clinical Department to the UKE. During 2004 a dramatic reduction of the occupancy rate had occurred that dropped below 30%. The cause was the changed situation in the public health system, e.g. the introduction of diagnosis related groups (DRG) that created economic problems especially for small and specialized hospitals. Due to the general economic pressure other hospitals completely stopped to transfer patients with tropical infections to the BNI and rather asked for treatment advice by telephone. Such transferred patients had previously made up one third of the occupancy. Decreasing revenues were also caused by shorter hospital stays of the patients and by the increasing possibilities for ambulatory treatment of tropical infections. Altogether this led to the accumulation of a considerable deficit of the Clinical Department that could not be compensated even by rigorous economy measures. A consulting company was not able to provide a reasonable solution to the problems and finally recommended the sale of the Clinical Department. After tender several offers were received and from several interested parties, the UKE was selected and a contract of sale was signed. Accordingly, the UKE took over the personnel, equipment and obligations of the Clinical Department. Due to the peculiarities of the German health system the UKE will now be able to increase its revenues within the next years sufficiently to outweigh all liabilities. It was essential for the BNI to ensure a continuously close cooperation with the Clinical Department within the transfer agreement. Outpatient clinic, travel medicine and vacci-

nation will remain within the BNI building, but the wards and the quarantine unit of the Clinical Department for patients with highly contagious infections are now located 7 km away on the UKE campus.

Under the given circumstances and the extreme financial pressure this was the best solution to secure the Clinical Department and its interaction with the BNI. Nevertheless, it is regrettable that after 105 years the entity of research institute and hospital originally founded by Bernhard Nocht could not be maintained. The Scientific Advisory Board had recommended maintaining the Clinical Department as a small research clinic. However, this concept could not be pursued due to the additional funding that it required. Due to the great public interest in all matters concerning the BNI the local media accompanied the process with many articles.

Cooperation with the German Federal Armed Forces Medical Service

Due to the increasing number of international peacekeeping missions of the German Federal Armed Forces, tropical medicine has obtained a high relevance for the German Armed Forces. It was therefore decided to establish a Tropical Medicine Unit at the BNI. An agreement for cooperation in the field of training, patient care and diagnostics research was signed on 19 August 2005. The Surgeon General of the German Armed Forces Medical Service, Admiral Dr. Karsten Ocker, came in person to the BNI to sign the agreement. Starting 2006 the Tropical Medicine Unit of the German Federal Armed Forces Medical Service occupies a wing of the former in-patient clinic at BNI.

Service

In the reporting period BNI received samples of suspected infections with highly contagious fever viruses from a growing number of countries. The emergency service of the BNI for rapid diagnosis was used 154 times in 2005. An agreement between BNI and the Hellenic Centre for Infectious Disease Control of the Greek Ministry of Health and Welfare secured the permanent availability of BNI's emergency diagnostic service for the Olympic Games in Athens in Summer 2004. The BNI was instrumental in the elucidation of a spectacular case of rabies virus transmission via solid organ transplantation. The central diagnostic unit conducted more than 45.000 tests in 2005 and was accredited according to DIN EN ISO 15189. The website for travel medicine of the BNI was visited more than 250.000 times in 2005.

Constructions

2005 saw the start of construction works for the urgently needed laboratory extension. The acquisition of more and better qualified space for research work is most important for the future of the institute. The historic building of 1914 by Fritz Schumacher provided sufficient space for the less than 80 employees of the time, but since many years the institute has been overcrowded and the shortness of of laboratories of higher biosafety levels has been an obstacle to use more grant money and to accommodate the necessary personnel.

After several years of complex planning and approval procedures the construction of an extension building on the site of the animal house could finally start in January 2005, 2 years later than originally planned. All contents of the animal house, including the albeit reduced mouse colony, had to be accommodated in the main building exacerbating the space distress. However, the prospect of more space in the not too far future helps bearing the situation. A great help in financing was the success of the BNI in securing a grant from the research infrastructures activity of FP6. This project EUTRICOD (European Centre for Training and Research on Imported and Highly Contagious Diseases) provides an additional funding of roughly 2 Mio Euro to establish BNI as a world-class facility for training and research in biomedicine.

Financial Matters

Again the BNI had to suffer from financial cuts due to the general economic situation in Germany. As in every year since 1996 it had to reduce its personnel by 1.5 % per annum with a corresponding shortening of funds. However, in recognition of the extraordinary success of BNI scientists in identification of the SARS coronavirus the research group on molecular diagnostics led by Dr. Drosten was permanently incorporated into the BNI that had been paid by grant money and the basic funding of the BNI increased accordingly. Annually 2.5 % of the total budget of the BNI are transferred to the *Deutsche Forschungsgemeinschaft* (German National Research Association, DFG), 245,000 Euro in 2005. As this amount has to be taken from flexible accounts, the relative decrease of accounts for scientific personnel and consumables is in fact much higher than 2.5 %. In return to this transfer to the DFG, the Institute is permitted to apply for grants from DFG. This procedure is an instrument of competition for research funds, which was successfully faced by the BNI. In the reporting period, scientists secured triple of the transferred sum in 23 grants from the DFG. Altogether the BNI received grant money worth more than 3.44 Mio. Euro in the year 2005. BNI members coordinate five and participate in 13 European consortia.

Personal Matters

Two leading scientists of the BNI retired in 2005. Professor Rolf D. Walter, Head of the Department of Biochemistry, retired in July, Professor Herbert Schmitz, Head of the Department of Virology in October. Fortunately both decided to pursue ongoing scientific projects as associated scientists. The BNI is thankful for their ongoing contribution. In an international selection procedure, Dr. Stephan Günther was appointed as the new head of the Department of Virology. Two new research groups on Clinical Virology were formed: Research Group Clinical Virology, headed by Dr. Christian Drosten and Research Group Infection Epidemiology, headed by Dr. Jürgen May. To provide additional manpower for urgent administrative and structural changes Mr. Udo Gawenda joined the BNI as an administrative manager. His first assignment was the realisation of the transfer of the Clinical Department. After this is completed his main task is now the realisation of an independent legal form for the BNI, a project that shall be completed in 2007.

Visitors

The Institute was again honoured by the visits of a number of VIP's. The First Mayor of the Free and Hanseatic City of Hamburg, Mr. Ole von Beust, visited the institute in February 2004, the Minister of Science and Health, Senator Jörg Dräger, PhD, in April 2004. The laying of the foundation stone of the extension wing gathered a large number of VIPs, among them again The First Mayor Ole von Beust, and the Federal Minister of Health, Mrs. Ulla Schmidt. More than 2000 citizens of Hamburg were attracted by the BNI during the long night of science in Hamburg in November 2005.

The Bernhard Nocht Medal was awarded to Professor Vincent Deubel, Institute Pasteur of Shanghai in June 2005 during the annual conference of the German Society for Tropical Medicine and International Health. This medal was originally endowed in 1925 by the Association of Friends of the Tropical Institute (*Vereinigung der Freunde des Tropeninstitutes Hamburg*) as an award for special merits in "research and control of tropical diseases" (*für Erforschung und Bekämpfung von Tropenkrankheiten).* Among the names of awardees are Bernhard Nocht, Albert Schweitzer, Gustav Giemsa, and Philip Manson Bahr. As from the inception the award is financed by the *Vereinigung der Freunde des Tropeninstituts Hamburg* and is jointly awarded by the BNI and the German Society for Tropical Medicine and International Health. Professor Deubel received the medal in recognition of his contributions to the research on tropical viruses.

Recognition

The work of members of the BNI again received appreciation in 2004 and 2005. An outstanding event was the award of Federal Merit Awards (Bundesverdienstorden) to four BNI scientists by the Federal Minister of Health, Ulla Schmidt. Dr. Klara Tenner-Racz and Prof. Paul Racz were honoured for their achievements in HIV research and the virologists Dr. Drosten and Dr. Günther for the identification of the SARS coronavirus in 2003. Dr. Drosten received several awards in 2004 for his innovative research in the field of molecular diagnostics. Prof. Gerd-Dieter Burchard was elected president of the German Society for Tropical Medicine and International Health. Dr. Eva Liebau was offered a professorship at the University of Münster. The BNI appreciates this recognition of her successful work, even though it resulted in her leaving the institute.

Acknowledgements

Two members of the Scientific Advisory Board left the Board in 2005 due to the end of their term of office. Professores Jürgen Heesemann and Philippe J. Sansonetti had been chairman and vice-chairman of the board. The BNI and – I myself in particular – are grateful for the time and effort they have devoted to the advancement of the BNI in these years.

The BNI thanks again its financiers, the Federal Ministry of Health and the Department of Health of the Free and Hanseatic City of Hamburg, for their continuous support of the work of the Bernhard Nocht Institute. The *Society of Friends* generously supported BNI with funds from private donations. All members of the BNI including the staff of the clinical department are commended upon their work in this turbulent period.

Hamburg, April 2006

Bernhard Fleischer

Awards for Members of the BNI

Awards in 2004

Dr. rer. nat. Zita Krnajski,
Department of Biochemical Parasitology
- *Gerhard Piekarski Award, German Society of Parasitology*

Dipl. Biol. Nicole Struck, Research Group Malaria II
- *Endeavour Australia Student Award, Australian Government*

Dr. med. Christian Drosten, Department of Virology
- *Glaxo-Smith Kline Award for Clinical Infectiology, German Society of Infectiology (06/2004)*
- *Abbot Diagnostics Award, European Society of Clinical Virology (09/2004)*
- *BioMerieux Diagnostic Award, German Society of Hygiene and Microbiology (09/2004)*
- *Postdoc Award of the Robert Koch Foundation (11/2004)*

Awards in 2005

Dr. med. Christian Drosten, Department of Virology
- *Federal Merit Award – Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. med. Stephan Günther, Department of Virology
- *Federal Merit Award – Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Prof. med. Dr. Paul Racz, Department of Pathology
- *Federal Merit Award – Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. med. Klara Tenner-Racz, Department of Pathology
- *Federal Merit Award – Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. Sonja Niknafs, Department of Immunology
- *Medac Dissertation Award, Friends of the University Medical Centre Hamburg-Eppendorf (12/2005)*

Offered Professorships

Prof. Dr. Eva Liebau,
Department of Biochemical Parasitology (2005)
- *Professor for Zoology, University of Münster (2005)*

Habilitations and Award of the Venia Legendi at the University of Hamburg

Privatdozent Dr. rer. nat. Peter Fischer,
Department of Helminthology (2004)

Privatdozent Dr. med. Peter Borowski,
Department of Virology (2005)

Best Thesis Award, Society of Friends of the Tropical Institute Hamburg

Dr. med. Thorsten Thye,
Department of Molecular Medicine (2005)

Dr. rer. nat. Zita Krnajski,
Department of Biochemical Parasitology (2004)

Vorwort

Am Beginn der Berichtsperiode 2004/2005 stand ein Verdachtsfall von Vogelgrippe bei einer Thailand-Reisenden, die am 2. Februar 2004 ins BNI eingeliefert wurde. Die Diagnostik des BNI konnte erwartungsgemäß nach wenigen Stunden Entwarnung geben. Dennoch sorgte der Fall für großes öffentliches Aufsehen bis hin zu kurzzeitigen Kurseinbrüchen bei börsennotierten Tourismusunternehmen. Wieder einmal war eine neue Infektionskrankheit plötzlich in das Bewusstsein der Öffentlichkeit getreten, eine Situation, in der sich das BNI bereits mehrfach als Kompetenzzentrum bewährt hat. Trotz dieser Kompetenz gelang es nicht, ausreichend Patienten für eine wirtschaftliche Auslastung der Klinischen Abteilung zu akquirieren. 2005 wurde deutlich, dass die kleine, hoch spezialisierte Einheit nur durch Eingliederung in eine größere Klinik erhalten werden kann – eine Entwicklung, die insbesondere den strukturellen Veränderungen im Gesundheitswesen geschuldet ist. Mit dem Ende der Berichtsperiode wurde die klinische Abteilung des BNI daher an das Universitätsklinikum Hamburg-Eppendorf (UKE) übertragen. Weitere herausragende Ereignisse waren der Beginn der Bautätigkeit für die lang geplante räumliche Erweiterung, der Abschluss eines Kooperationsvertrages mit dem Sanitätsdienst der Bundeswehr und die Verleihung von vier Bundesverdienstkreuzen an BNI-Mitglieder.

Das Bernhard-Nocht-Institut

Seit seiner Gründung am 1.10.1900 als *Institut für Schiffs- und Tropenkrankheiten* ist das BNI Deutschlands größtes Institut für Forschung auf dem Gebiet der Tropenmedizin und hat seither Forschung, Lehre und Patientenversorgung unter einem Dach vereint. Als Institut der Leibniz-Gemeinschaft, in der Institute mit überregionaler wissenschaftspolitischer Bedeutung vereint sind, wird es gemeinsam nach Artikel 91b des Grundgesetzes von Bund und Ländern finanziert. Träger des Institutes sind das Bundesministerium für Gesundheit und die Behörde für Wissenschaft und Gesundheit der Freien und Hansestadt Hamburg, deren Dienststelle es ist. Das Institut hat zur Zeit (2006) rund 280 Mitarbeiter, inklusive der Stipendiaten, Diplom-Studenten und Praktikanten. Es verfügt in seiner Grundausstattung über 40 Wissenschaftlerstellen für die Forschung, das wissenschaftliche Personal umfasst inklusive der Drittmittel-finanzierten Stellen rund 90 Personen.

Aufgaben des BNI

Als Zentrum für Tropenmedizin in Deutschland ist das BNI der Forschung, der Ausbildung und der Gesundheitsversorgung auf dem Gebiet der tropischen Infektionskrankheiten des Menschen gewidmet. Hauptaufgabe des BNI ist die Erforschung dieser Erkrankungen, um Mittel und Wege für ihre Bekämpfung aufzuzeigen. Zusätzliche Aufgaben liegen in der Ausbildung von Ärzten und Studenten und in der mittelbaren Versorgung von Patienten mit tropischen Infektionen.

Das BNI führt als Nationales Referenzzentrum für tropische Infektionserreger eine Diagnostik zum Nachweis von speziellen tropischen Krankheitserregern durch, die überregional in Anspruch genommen wird. Es unterhält zum Nachweis und zur Erforschung von hochinfektiösen Erregern wie z.B. hämorrhagischen Fieberviren ein Hochsicherheitslabor der Stufe 4. Bis Ende 2005 war eine klinische Abteilung mit 62 Betten und einer Ambulanz, die der Versorgung von Kranken mit tropischen und anderen Infektionskrankheiten dienen, integraler Teil des Institutes. Aus ökonomischen Gründen musste die Klinik organisatorisch an das UKE angegliedert werden, wobei Ambulanz, Impfsprechstunde und reisemedizinische Beratungsstelle weiterhin am Standort Bernhard-Nocht-Straße angesiedelt sind und eine Kooperation mit kurzen Wegen ermöglichen.

Das BNI zeigt ein großes Engagement in der Lehre: Es veranstaltet jährlich verschiedene Kurse mit Bezug auf die Tropenmedizin, u.a. einen dreimonatigen Diplomkursus in Tropenmedizin und Parasitologie für die Zusatzbezeichnung „Tropenmedizin“ für Ärzte, der bei der American Society for Tropical Medicine and Hygiene akkreditiert ist. Dreizehn Hochschullehrer des BNI führen derzeit Lehrveranstaltungen in den Fachbereichen Medizin, Biologie und Chemie der Universität Hamburg durch. Im Berichtszeitraum wurden 51 Diplomarbeiten und Dissertationen abgeschlossen. Drei Mitglieder des Instituts haben C4-Professuren (für Molekulare Parasitologie, für Immunologie und für Tropenmedizinische Grundlagenforschung) im Fachbereich Medizin inne.

Wissenschaftliches Programm

Die Forschung des BNI konzentriert sich auf die Charakterisierung der Erreger-Wirt-Interaktion bei tropischen Infektionserregern mit folgenden Schwerpunkten:

1. die zelluläre und molekulare Charakterisierung der Erreger,
2. die Wirtsreaktion auf diese Erreger und ihre schützende oder pathologische Rolle,
3. die Mechanismen der Pathogenese und der Erkrankung.

Bei all diesen Untersuchungen wird auf die Relevanz für die Bekämpfung tropischer Infektionen Wert gelegt sowie auf die Möglichkeit, tropische Infektionen als Paradigmen grundlegender Prinzipien in Biologie und Medizin zu behandeln.

Um diese Arbeiten durchführen zu können, verfügt das BNI über Abteilungen und Arbeitsgruppen mit unterschiedlicher Spezialisierung und Schwerpunktsetzung, die in drei wissenschaftlichen Sektionen (Parasitologie, Medizinische Mikrobiologie und Tropenmedizin)

zusammengefasst sind. Abteilungen werden für längere Zeiträume bestehen, Arbeitsgruppen sollen je nach wissenschaftlicher Notwendigkeit ersetzt werden und dienen der Flexibilität der wissenschaftlichen Arbeit. Die historische Verbindung mit der Klinischen Abteilung, die aktiv an den Forschungsarbeiten beteiligt ist, hat sich bewährt, da die in Hamburg behandelten Patienten anders als Patienten in den Tropen meist nur mit einem Erreger infiziert sind und hier mit hochtechnologischen Methoden auch über längere Zeiträume hinweg untersucht werden können. Ein großer Teil der klinischen Forschung findet allerdings in den Endemiegebieten der Tropen statt, mit denen das BNI langjährige Kooperationsbeziehungen unterhält.

Schwerpunkte der wissenschaftlichen Arbeiten

Wegen seiner begrenzten finanziellen Möglichkeiten konzentriert sich das BNI in seiner Forschungsarbeit auf tropische Erreger, die durch die Zahl der von ihnen Infizierten bedeutend oder beispielhaft für grundlegende Prinzipien in Biologie und Medizin sind. Einige beispielhafte Erkrankungen werden von Wissenschaftler aus verschiedenen Abteilungen oder Arbeitsgruppen institutsübergreifend bearbeitet (zur Zeit Malaria, Filariasis, Amöbiasis und Leishmaniasis), daneben sind tropische Fieberviren, Trypanosomen und HIV/AIDS wichtige Themen der Forschung.

Die **Malaria** ist inzwischen das größte Forschungsgebiet des BNI, in dem die Arbeiten von der molekularen Charakterisierung von Bestandteilen der Plasmodien bis hin zu klinischen Studien zur Therapie der schweren Malaria bei Kindern in Ghana reichen. Schlüsselenzyme des Glutathion-Metabolismus und der Polyaminsynthese der Plasmodien werden molekular untersucht, um neue Ansatzpunkte für die Chemotherapie zu finden. Der vollständige Zyklus von *Plasmodium berghei* in der Maus ist vorhanden und kann verwendet werden, um Sporozoiten und Leberstadien des Erregers zu untersuchen. So wird die Resistenz der infizierten Leberzellen gegen Apoptose analysiert und das Verhalten des Immunsystems in der Frühphase der Infektion in der Leber, aber auch während der Blutphase. Weitere Arbeiten betreffen die molekularen Mechanismen der Invasion der Plasmodien und des Transportes von Plasmodienmolekülen in infizierten Erythrozyten. Parameter der Pathogenese der schweren Malaria werden bei infizierten Mäusen und bei Patienten analysiert. Studien in Ghana betreffen die Bestimmung von Genen, die Empfänglichkeit oder Resistenz gegenüber schwerer Malaria tropica vermitteln, und – im Rahmen der deutschen Malaria-Initiative – die Wirksamkeit der intermittierenden Therapie mit Sulfadoxin-Pyromethamin bei Malaria. Eine groß angelegte klinische Studie zur Erprobung eines Malariaimpfstoffes wird an der Forschungsstation KCCR in Ghana durchgeführt (s. u.).

Die **Amöbiasis** ist seit 1988 als Institutsschwerpunkt eingeführt, als im BNI der eigentliche Erreger der Amöbenruhr, die pathogene Amöbenart *Entamoeba histolytica* entdeckt wurde, und von häufig auftretenden, aber apathogenen Art *E. dispar* abgegrenzt werden konnte. Die Arbeiten decken Aspekte der Biologie und Pathogenität von *E. histolytica*, ab und reichen bis zu neuen Methoden der Diagnostik und Therapie. Die aktuellen Arbeiten beschäftigen sich mit der Identifizierung und Charakterisierung von Molekülen der Amöben, die für die Pathogenese verantwortlich sind und mit der Genom-Organisation der Amöben, insbesondere dem Vergleich zwischen *E. histolytica* und *E. dispar.* Epidemiologische und klinische Studien werden in Zusammenarbeit mit dem *Hué Medical College* in Vietnam, durchgeführt. Ein Impfstoff wird entwickelt, dessen erste Prüfungen im Tierversuch bereits erfolgreich verlaufen sind.

Die Forschung an **Filarien** am BNI reicht bis in die 60er Jahre zurück und betrifft insbesondere die Flussblindheit oder Onchocerciasis, aber auch die lymphatische Filariasis. Auch hier reichten die Arbeiten vom molekularen Modelling zur Gewinnung von neuen Chemotherapeutika bis zur Patientenstudie in den Tropen. Sezernierte Proteasen der Würmer und Mikrofilarien werden kloniert und charakterisiert, da sie für die Wanderung des sich entwickelnden Wurmes und der Mikrofilarien essentiell sind und Angriffspunkte für therapeutische Strategien bieten könnten. Ebenso werden spezielle Stoffwechselwege der Würmer untersucht, um neue spezifische Chemotherapeutika zu finden. So wurden vor einiger Zeit von Wissenschaftlern des BNI intrazelluläre Bakterien der Filarien als ein neues Ziel für eine Chemotherapie identifiziert. Die immunologischen Untersuchungen betreffen die Mechanismen der Abwehr der Würmer im Tiermodell und die Charakterisierung der starken spezifischen Immunsuppression gegen Antigene des Wurmes bei Patienten mit generalisierter Onchozerkose. Wirtsgene, die für die unterschiedliche Ausprägung der Infektion verantwortlich sind, werden in einer großen Studie in der Umgebung von Kumasi identifiziert. Kandidatenproteine für Impfstoffe gegen Filarien werden in Tiermodellen erprobt.

Die Erforschung der **hämorrhagischen Fieberviren** hat sich zu einem weiteren Schwerpunkt des Instituts entwickelt. Untersuchungen betreffen die molekularen Replikationsmechanismen des Lassavirus, die Verbreitung des Virus in Westafrika und Mechanismen der Pathogenese des Lassa-Fiebers. Neue diagnostische Methoden für hämorrhagische Fieberviren werden erprobt und in der Diagnostik eingesetzt. Die Virologen des BNI, die in mehrere europäische Netzwerke eingebunden sind, agieren europaweit als Ansprechpartner für importierte Virusinfektionen. Der neue Leiter der Abteilung Virologie, PD Dr. Stephan Günther, ist Koordinator eines EU-geförderten Netzwerkes für die Diagnostik viraler hämorrhagischer Fieber.

AIDS-Forschung hat über zwanzigjährige Geschichte am BNI, da bereits 1982 die ersten Patienten mit den damals „exotischen“ Folgeinfektionen von HIV/AIDS am BNI behandelt wurden. In den Abteilungen Pathologie und Virologie werden die Verteilung des HIV im lymphatischen Gewebe, die Verbreitung des Virus nach Infektion über die Schleimhäute und die Bildung neutralisierender Antikörper gegen das Glykoprotein gp120 untersucht. Ein von der Europäischen Union finanziertes Konsortium von Wissenschaftlern aus mehreren europäischen Ländern wird von Prof. Racz geführt und arbeitet über neue Wege der Impfung gegen HIV.

Kooperative Forschung in den Tropen

Das BNI führt zahlreiche Forschungsprojekte in den Tropen durch, mehrere haben zu dauerhaften Partnerschaften geführt. Allen voran sei das *Kumasi Centre for Collaborative Research in Tropical Medicine* (KCCR) genannt, ein gemeinsames Projekt des BNI und der Medizinischen Fakultät der Universität von Kumasi in Ghana. Durch einen Staatsvertrag zwischen der Freien und Hansestadt Hamburg und der Republik Ghana wurde 1997 die Errichtung des KCCR vereinbart. Alle wissenschaftlichen Projekte werden gleichberechtigt von einem Mitarbeiter des Tropeninstituts und einem ghanaischen Wissenschaftler geleitet. Das KCCR soll sich langfristig zu einem Zentrum der internationalen Zusammenarbeit entwickeln, denn auch Wissenschaftler anderer Institutionen sind eingeladen, zusammen mit ghanaischen Partnern dort Forschungsprojekte durchführen. Das KCCR ist bemüht, den wissenschaftlichen Nachwuchs zu fördern, Ärzten und Wissenschaftlern die Weiterbildung und internationalen Austausch zu ermöglichen. Gleichzeitig werden im Rahmen der Forschungsprojekte Stellen für ghanaische Wissenschaftler geschaffen. Durch die vielen überwiegend aus Drittmitteln finanzierten Projekte hat sich das KCCR in den letzten Jahren stark vergrößert, es beschäftigt inzwischen mehr als 40 feste Angestellte und eine große Zahl temporärer Mitarbeiter. Es verfügt seit 2 Jahren über ein Ensemble von eigenen Gebäuden, die mit Mitteln der Volkswagen-Stiftung, der Träger in Bonn und Hamburg und der Vereinigung der Freunde des Tropeninstituts Hamburg errichtet worden waren.

Andere langfristige Kooperationsprojekte mit offiziellen Vereinbarungen werden mit der Medizinischen Fakultät der Universität von Hué, Vietnam, dem Central Drug Research Institute in Lucknow, Indien, und mit dem Uganda Virus Research Institute in Entebbe durchgeführt.

Ereignisse in 2004 und 2005

Eine Chronik besonderer Ereignisse der Zeit dieses Berichtes ist im Anhang zu finden.

Verkauf der Klinischen Abteilung

Eine Entwicklung, die das BNI nachhaltig veränderte, war der Verkauf der Klinischen Abteilung an das Universitätsklinikum Hamburg-Eppendorf (UKE). Seit 2004 war die Belegung der Klinikbetten dramatisch gesunken. Der Grund lag im Strukturwandel im Gesundheitssystems, u.a. der Einführung des neuen Fallpauschalensystems, das besonders auf kleine und hoch spezialisierte Einrichtungen wie die Klinische Abteilung negative Auswirkungen hat. Durch die zunehmende Konkurrenz um Patienten verringerten sich in dramatischer Weise die Überweisungen aus anderen Kliniken, die früher zur Abklärung und Spezialbehandlung erfolgten und bis zu einem Drittel der Belegung ausgemacht hatten. Die zunehmenden ambulanten Behandlungsmöglichkeiten und die kürzere Verweildauer der Patienten bei Tropenerkrankungen senkten die Belegungszahlen zusätzlich. Dies führte zu deutlichen Einnahmerückgängen seit 2003, die trotz rigoroser Sparmaßnahmen erhebliche finanzielle Verluste zur Folge hatten. Eine Beraterfirma wurde engagiert, die allerdings keine grundlegenden Verbesserungen der Wirtschaftlichkeit der Klinik erreichen konnte und daher die Übertragung an einen in Hamburg ansässigen Krankenhausträger empfahl. Nach Ausschreibung wurde aus den Angeboten verschiedener Krankenhäuser das UKE als Träger ausgewählt. Der Kaufvertrag beinhaltete die Übernahme des Personals und der aufgelaufenen Verluste der Klinik, so dass das BNI die Klinik ohne finanzielle Einbußen abgeben konnte. Durch Übernahme des Budgets der Klinik wird das UKE in absehbarer Zeit diese Verluste durch vermehrte Einnahmen wieder ausgleichen können. Für das BNI von größter Wichtigkeit war die Erhaltung der engen Interaktion von Institut und Klinik in Forschung, Lehre und Diagnostik. Der Vertrag regelte auch die Kooperation mit dem UKE. Ambulanz, Impfsprechstunde und Reisemedizin werden am Standort Bernhard-Nocht-Straße betrieben, die stationäre Versorgung und die Quarantäne-Einheit für Patienten mit hochkontagiösen Infektionen werden als „Sektion Tropenmedizin Bernhard Nocht“ in das UKE transferiert. Prof. Burchard als Leiter der Sektion wird zugleich Leiter einer vom BNI finanzierten Arbeitsgruppe Klinische Forschung im BNI.

Unter den gegebenen Umständen war dieses die beste Lösung, die Existenz der Klinischen Abteilung und ihre Interaktion mit der Forschung konnten gesichert werden. Dennoch ist es sehr betrüblich, dass nach mehr als 105 Jahren die von Bernhard Nocht gegründete Einheit von Forschung und stationärer Krankenversorgung im BNI nun ein Ende haben musste. Die vom wissenschaftlichen Beirat favorisierte Vorstellung, die klinische Abteilung als kleine Forschungsklinik zu

erhalten, ließ sich wegen der dafür benötigten erhöhten Forschungszuschüsse der Träger nicht realisieren. Wegen des großen öffentlichen Interesses am BNI wurde dieser Prozess von den Medien begleitet, was zu nicht zutreffenden Mutmaßungen führte, demnach das gesamte BNI Teil des UKE würde oder der Erweiterungsbau nicht weitergebaut werden könne.

Kooperation mit dem Sanitätsdienst der Bundeswehr

Die seit langem vorbereitete Kooperation der Bundeswehr mit dem BNI auf dem Gebiet der Tropenmedizin wurde mit der feierlichen Unterzeichnung eines Kooperationsvertrages am 19. August 2005 besiegelt. Der Inspekteur des Sanitätsdienstes der Bundeswehr, Herr Admiraloberstabsarzt Dr. Karsten Ocker, kam eigens zur Unterzeichnung ins BNI. Durch die zunehmenden internationalen Aufgaben in Friedensmissionen der Bundeswehr hat die Tropenmedizin eine besondere Bedeutung für die Bundeswehr erlangt. Der Sanitätsdienst der Bundeswehr hatte daher beschlossen, eine Zusammenarbeit in Klinik, Diagnostik und Forschung mit dem BNI als Deutschem Zentrum für Tropenmedizin zu vereinbaren. Der Fachbereich Tropenmedizin des Bundeswehrkrankenhauses Hamburg hat Anfang 2006 im BNI seine Arbeit aufgenommen.

Service

Wiederholt musste das BNI seine Kapazität als diagnostisches Zentrum für hochkontagiöse Erreger zur Verfügung stellen. Insbesondere nahm die Zahl der aus dm Ausland eingesandten Proben zur diagnostischen Abklärung von tropischen Virusinfektionen zu. Im Jahre 2005 wurden 154 Notfalluntersuchungen bei Verdacht auf virales hämorrhagisches Fieber durchgeführt. Das BNI hält wegen der hohen Dringlichkeit in diesen Fällen einen Notdienst rund um die Uhr vor um eine schnelle differentialdiagnostische Klärung zu gewährleisten. Die Proben werden üblicherweise im Hochsicherheitslabor untersucht, was einen hohen Aufwand weit über die Routine hinausgehend bedeutet. Anlässlich der Olympischen Spiele in Griechenland in 2004 wurde ein Vertrag zwischen BNI und dem *Hellenic Centre for Infectious Disease Control* des griechischen Gesundheitsministeriums abgeschlossen, der von Juni bis Oktober 2004 die ständige Verfügbarkeit des BNI zur schnellen Notfalldiagnostik sicherstellte. Das BNI war zudem maßgeblich beteiligt an der Aufklärung eines spektakulären Falles von Tollwut-Übertragung durch Organtransplantation. Die Mikrobiologische Zentraldiagnostik führte in 2005 mehr als 45.000 Einzeluntersuchungen an bundesweit eingesandten Proben durch. Die diagnostischen Labors wurden 2005 nach DIN EN ISO 15189 akkreditiert. Die Webseiten des BNI und des Reisemedizinischen Zentrums wurden in 2005 mehr als 250.000 mal besucht.

Bautätigkeiten

Anfang 2005 begannen nach mehrjähriger Planungszeit die Arbeiten am Erweiterungsbau auf dem Gelände des Tierhauses, der für die Zukunft des BNI von entscheidender Bedeutung ist. Insbesondere die Knappheit an Sicherheitslabors gefährdet bereits den Beginn neuer Projekte, neue Arbeitsgruppen konnten nicht aufgenommen werden. Bereits zum Jahreswechsel 2004 war das alte Tierhaus geräumt und die Labors inklusive der Tierhaltung in das Hauptgebäude verlegt worden. Jedoch lässt die Aussicht, in nun absehbarer Zeit endlich eine adäquate Raumausstattung zu bekommen, die daraus resultierende Enge leichter ertragen.

Ein besonderer Erfolg war die Bewilligung von zusätzlichen Mitteln aus dem Exzellenzprogramm zur Förderung von Forschungsinfrastrukturen der Europäischen Kommission. Damit wird das BNI zu einem europäischen Zentrum für importierte und hochkontagiöse Erkrankungen ausgebaut (*European Centre for Training and Research on Imported and Highly Contagious Diseases*, EUTRICOD). Der Zuschuss beträgt 10 % der geschätzten Gesamtkosten für Baumaßnahmen und ermöglicht im Sinne des Exzellenzgedankens zusätzliche Ausstattung der Forschungsanlagen.

Finanzen

Auch in diesem Berichtszeitraum blieb das BNI auf Grund der schwierigen finanziellen Lage der öffentlichen Haushalte von Sparmaßnahmen nicht verschont. Es musste wiederum jährlich jeweils 1,5% seiner Stellen abbauen mit entsprechender Kürzung der Mittel. Allerdings erhöhten die Träger des BNI auf Grund des Erfolges bei der Identifizierung des SARS Coronavirus die Grundfinanzierung des BNI zur dauerhaften Etablierung der von Dr. Drosten geleiteten Arbeitsgruppe „Diagnostische Verfahren“ ab dem Jahr 2005, die bislang aus Drittmitteln finanziert worden war.

Außerdem führte das BNI wie in jedem Jahr 2,5% seines Gesamtetats an die Deutsche Forschungsgemeinschaft (DFG) ab, 245.000 Euro in 2005. Da dieser Betrag nur aus flexiblen Titeln entnommen werden kann, betrifft dies überproportional die Grundausstattung für wissenschaftliches Personal und für Sachmittel. Im Gegenzug hat das Institut die Möglichkeit, bei der DFG auch auf seinen Hauptarbeitsgebieten Anträge zu stellen. Diesem Instrument des Wettbewerbs um Forschungsgelder hat sich das BNI wiederum mit Erfolg gestellt: in 23 DFG-Projekten wurde mehr als das Dreifache der abgeführten Summe wieder eingeworben. Auch insgesamt war das BNI 2005 mit Einnahmen von 3,44 Mio. Euro erfolgreich bei der Einwerbung von Drittmitteln. Fünf EU-Konsortien werden derzeit von BNI Mitglieder koordiniert und im Berichtszeitraum arbeiteten BNI-Wissenschaftler an 13 EU-geförderten Projekten mit. Wegen der knapper werdenden Mittel gibt es Wettbewerb auch innerhalb des BNI: Die Mittel

für die Arbeitsgruppen werden nach Leistungen, gemessen an Publikationsaktivität und Drittmitteleinwerbung, verteilt.

Personalia

Zwei führende Wissenschaftler des BNI gingen nach langer Tätigkeit am BNI in den Ruhestand. Prof. Dr. Rolf D. Walter, Leiter der Abteilung Biochemie, ging zum 1. August 2005, Prof. Dr. Herbert Schmitz, Leiter der Abteilung Virologie, zum 1. November 2005. Beide haben über viele Jahre wesentlich zum Gelingen der Mission des BNI beigetragen. Das BNI ist ihnen zu großem Dank verpflichtet. Es ist erfreulich, dass beide Abteilungsleiter dem BNI weiter verbunden bleiben und im Institut Projekte weiterführen werden, wie dies schon fast Tradition am BNI geworden ist.

Für die Abteilung Virologie wurde nach internationaler Ausschreibung PD Dr. Stephan Günther als Leiter und Nachfolger von Prof. Schmitz berufen. Ende 2004 wurde eine neue Arbeitsgruppe Infektionsepidemiologie unter Leitung von PD Dr. Jürgen May eingerichtet, Ende 2005 eine Arbeitsgruppe Klinische Virologie unter Leitung von Dr. Christian Drosten. Als Unterstützung für die notwendigen administrativen und strukturellen Veränderungen, die auf das BNI warten, kam im April 2005 Herr Udo Gawenda als Kaufmännischer Geschäftsführer an das BNI. Seine Aufgabe war zunächst die Durchführung des Verkaufs der Klinischen Abteilung und ist nun besonders das Projekt der Verselbständigung des BNI, das nun im Jahre 2007 endgültig abgeschlossen werden soll.

Besucher

Das Institut empfing wiederum eine Reihe von hochrangigen Besuchern: Den Ersten Bürgermeister der Freien und Hansestadt Hamburg, Herrn Ole von Beust, im Februar 2004, den Senator für Wissenschaft und Gesundheit der Freien und Hansestadt Hamburg, Herrn Jörg Dräger, PhD im April 2004. Zur Grundsteinlegung für den Erweiterungsbau versammelte sich eine große Zahl von VIPs in der Baugrube, darunter Gesundheitsministerin Ulla Schmidt, der Erste Bürgermeister Ole von Beust, Staatsrat Dietrich Wersich, Alt-Bürgermeister und MdB Ortwin Runde, der ehemalige Direktor des BNI, Prof. Hans-Harald Schumacher, der Chefarzt des Bundeswehrkrankenhauses, Oberstarzt Dr. Ulrich Philipp und der Ärztlichen Direktor des UKE, Prof. Jörg Debatin. Mehr als 2000 Besucher, alt und jung, besuchten das BNI während der ersten Hamburger Nacht des Wissens am 29. November 2005.

Die traditionsreiche Bernhard-Nocht-Medaille, die gemeinsam vom BNI und der DTG verliehen wird, wurde im Juni 2005 im Rahmen der Hamburger Tagung der DTG an den französischen Virologen Prof. Vincent Deubel überreicht. Der Direktor des Institut Pasteur in Shanghai erhielt die Medaille für seine Verdienste um die Erforschung tropischer Virusinfektionen.

Anerkennung

Herausragend war die Verleihung von vier Bundesverdienstorden im Dezember 2005 an Mitglieder des BNI: Dr. Klara Tenner-Racz und Prof. Paul Racz für die langjährigen exzellenten Arbeiten zur Vermehrung des HIV im Lymphknoten sowie Dr. Christian Drosten und PD Dr. Stephan Günther für die Entdeckung des SARS-Coronavirus und die schnelle Etablierung eines diagnostischen Nachweises. Prof. Gerd-Dieter Burchard, Leiter der Klinischen Abteilung, wurde zum Präsidenten der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit gewählt, deren Geschäftsstelle seit Jahren im BNI angesiedelt ist. Ein Ruf für Frau Dr. Eva Liebau auf eine Professur an der Universität Münster war eine Anerkennung der erfolgreichen Arbeiten am BNI, auch wenn er leider zum Verlust dieser erfolgreichen Wissenschaftlerin führte.

Danksagung

Zwei Mitglieder des wissenschaftlichen Beirates des BNI schieden turnusgemäß aus: der langjährige Vorsitzende Prof. Jürgen Heesemann und sein Stellvertreter Prof. Philippe J. Sansonetti. Sie haben dem BNI und mir selbst in Zeiten der Evaluation und finanzieller Schwierigkeiten mit Rat und Tat beigestanden. Das Institut ist ihnen für die Zeit und Mühe dankbar, die sie dem Vorankommen des BNI gewidmet haben. Den Trägern des BNI, der Behörde für Umwelt und Gesundheit der Freien und Hansestadt Hamburg und dem Bundesministerium für Gesundheit sei an dieser Stelle wieder für ihr Engagement und ihre Unterstützung des BNI gedankt. Der Vereinigung der Freunde des Tropeninstitutes e.V. soll für die großzügige Unterstützung gedankt werden, die aus privaten Spenden stammt. Allen Mitarbeiterinnen und Mitarbeitern des Institutes einschließlich der Klinischen Abteilung sei für die nicht immer unter einfachen Bedingungen erbrachte Leistung gedankt.

Hamburg, im April 2006

Bernhard Fleischer

Preise für Mitglieder des BNI

Auszeichnungen 2004

Dr. rer. nat. Zita Krnajski
- *Gerhard-Piekarski-Preis der Deutschen Gesellschaft für Parasitologie*

Dipl. Biol. Nicole Struck
- *Endeavour Australia Student Award, Australian Government*

Dr. med. Christian Drosten
- *Glaxo-Smith Kline Förderpreis für Klinische Infektiologie der Deutschen Gesellschaft für Infektiologie (06/2004)*
- *Abbot Diagnostics Award der Europäischen Gesellschaft für klinische Virologie (09/2004)*
- *BioMerieux Diagnostikpreis der Deutschen Gesellschaft für Hygiene und Mikrobiologie (09/2004)*
- *Postdoktorandenpreis der Robert Koch-Stiftung (11/2004)*

Auszeichnungen 2005

Dr. med. Christian Drosten, Abteilung für Virologie
- *Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. med. Stephan Günther, Abteilung für Virologie
- *Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Prof. med. Dr. Paul Racz, Abteilung für Pathologie
- *Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. med. Klara Tenner-Racz, Abteilung für Pathologie
- *Verdienstorden der Bundesrepublik Deutschland (12/2005)*

Dr. Sonja Niknafs, Abteilung für Immunologie
- *Medac-Promotionspreis des Freundes- und Förderkreises des UKE (12/2005)*

Berufungen

Prof. Dr. Eva Liebau, Abteilung für Biochemie (2005)
- *C3-Professur für Zoologie, Universität Münster (2005)*

Habilitationen und Erlangung der Venia legendi an der Universität Hamburg

Privatdozent Dr. rer. nat. Peter Fischer, Abteilung für Helminthologie (2004)

Privatdozent Dr. med. Peter Borowski, Abteilung für Virologie (2005)

Doktorandenpreis der Vereinigung der Freunde des Tropeninstituts Hamburg e.V.

Preisträger 2005: Dr. med. Thorsten Thye, Abteilung für tropenmedizinische Grundlagenforschung

Preisträgerin 2004: Dr. rer. nat. Zita Krnajski, Abteilung für Biochemie

Parasitology Section

Selected Scientific Projects
Ausgewählte wissenschaftliche Projekte

Parasitology Section

Chairman's Summary

The Parasitology Section combines the Department of Molecular Parasitology, the Department of Biochemistry and a number of research groups, working on various parasites of medical importance. Emphasis was given to amoebiasis, leishmaniasis and malaria, three protozoan diseases with high impact on morbidity and mortality in most tropical and subtropical countries. (Selected projects are described in the following reports).

Work on amoebiasis was performed in the **Department of Molecular Parasitology**. As part of an international consortium to sequence the *E. histolytica* genome, members of the Department have analysed and annotated the extraordinary large number of *E. histolytica* genes coding for antioxidant and proteolytic enzymes. Antioxidant enzymes are important to protect the parasite from oxidative damage during invasion of the human host, whereas proteolytic enzymes and in particular cysteine proteases constitute major pathogenicity factors, which are responsible for the extraordinary high capacity of *E. histolytica* to destroy human tissues. Interestingly, the *E. histolytica* genome was found to contain more than 80 different protease genes, the majority of which encode cysteine proteases (Iris Bruchhaus). In addition to genomic research, studies on the mechanism of gene silencing in *E. histolytica* was performed in order to extend the currently limited repertoire for the analysis of gene functions in this parasite (Henriette Irmer). Amoebic liver abscess is one of the most severe clinical outcomes of *E. histolytica* infection. Interestingly, this disease preferentially develops in males (>80%). A new animal model was established showing similar gender differences as found in humans and may allow to better dissect the mechanisms responsible for amoebic liver abscess development (Hannelore Lotter).

Two groups of the Parasitology Section have participated in Leishmania research. The group headed by **Joachim Clos** identified a regulator of the *Leishmania* cell cycle, LdGF1, which controls the G_0 to G_1 transition, i.e. the release from growth arrest. During a systematic screening, a novel Miltefosine resistance marker gene was discovered, coding for a 299-kD protein that is unrelated to previously known effectors of therapy resistance. The ongoing studies on the function of *Leishmania* heat shock proteins were extended to an atypical energy-dependent protease, HSL-V. Initial results indicate an essential and non-redundant function of HSL-V, which has no homologue in mammals and most other eukaryota. The group of **Martin Wiese** has concentrated on *Leishmania mexicana* mitogen-activated protein (MAP) kinase pathways and their role in parasite proliferation, differentiation and flagellar morphogenesis. The genome of *L. mexicana* contains various genes coding for different MAP kinases and their respective activators (MKK). The potential of the encoded proteins as drug targets to treat leishmaniasis is currently investigated.

Research on malaria is currently being performed in all three sections of the institute. Within the Parasitology Section, the **Department of Biochemistry** (Rolf D. Walter) focuses on metabolic pathways within the malaria parasite, which are distinct from those in the human host. In this respect, the assessment and validation of the polyamine metabolism as a target for chemotherapy has been continued and promising enzyme inhibitors have been validated as drug candidates (Kai Lüersen). Novel approaches for malaria therapy are offered by targeting of vitamin B1 and B6, the syntheses of both were recently identified in the malaria parasite (Carsten Wrenger). Further, in detail experimental studies on the only glutathione S-transferase of *P. falciparum* revealed the existence of two distinct cooperative phenomena, which modulate the interaction of the enzyme with glutathione and the parasitotoxic hemin (Eva Liebau).

Survival of intracellular parasites depends on their ability to circumvent apoptosis of the host cell. Using the rodent parasite *P. berghei* as a model system **Volker Heussler** and co-workers investigated survival strategies of *Plasmodium parasites* in hepatocytes from entry of sporozoites to the release of merozoites. In course of their ongoing studies they could show that during the first two days of infection the parasite protects host cells from apoptosis, whereas it induces apoptosis on the third day followed by the release of merozoites. Interestingly, intravital microscopy revealed that the release of merozoites is not simply the result of rupture of infected hepatocytes as previously thought. In contrast, the infected hepatocytes form long extensions called merosomes, which allow targeted release of merozoites across the endothelial cell-layer directly into the bloodstream.

Focusing on the secretion and invasion machinery of *Plasmodium falciparum* the group of **Tim Gilberger** was able to conclusively visualize the Golgi apparatus in the parasite. This membranous structure is the central hub of the eukaryotic secretory machinery and plays a pivotal role in protein modification, processing and sorting. Members of the group identified and characterized a novel Golgi marker protein termed GRASP. They used a GFP-tagged version in transgenic parasites to analyse the spatial organization and biogenesis of this organelle.

Apart from protozoan research, field studies were performed to characterize Simulium species that are responsible for onchocerciasis transmission in Africa. The aim of this work is to identify genetic markers to better distinghuish between those insect vectors that are able to transmit *Onchocerca volvulus* and those that do not. The results may help improve onchocerciasis control strategies (Andreas Krüger).

Egbert Tannich

Zusammenfassung des Sprechers

Die Sektion Parasitologie umfasst die Abteilung für Molekulare Parasitologie, die Abteilung für Biochemie sowie verschiedene Arbeitsgruppen, die über unterschiedliche medizinisch bedeutsame Parasiten arbeiten. Schwerpunkte waren Arbeiten zur Amöbiasis, Leishmaniasis und Malaria, drei der wichtigsten Humanparasitosen mit erheblichem Einfluss auf Morbidität und Mortalität in vielen tropischen und subtropischen Ländern. (Ausgewählte Projekte sind in den folgenden Beiträgen dargestellt).

Die Arbeiten zur Amöbiasis wurden in der **Abteilung für Molekulare Parasitologie** durchgeführt. Als Teil eines Konsortiums zur Sequenzierung des *E. histolytica* Genoms haben Mitglieder der Abteilung die ungewöhnlich große Zahl von Genen, die für Antioxidantien und proteolytische Enzyme kodieren, charakterisiert und annotiert. Antioxidantien benötigt der Parasit, um sich während der Invasion in das Gewebe vor Sauerstoffradikalen und anderen aggressiven Molekülen zu schützen. Dem gegenüber spielen die proteolytischen Enzyme, und hier vor allem die Cystein-Proteinasen, eine wichtige Rolle bei der Parasiten-induzierten Gewebsschädigung. Insgesamt fanden sich im Amöbengenom mehr als 80 Protease-Gene, von denen mehr als die Hälfte für Cystein-Proteasen kodieren (Iris Bruchhaus). Zusätzlich zur Genomforschung wurden Arbeiten über den Mechanismus der Geninaktivierung in *E. histolytica* durchgeführt mit dem Ziel der besseren genetischen Beeinflussung des Parasiten. Der Amöbenleberabszess ist eine der gefürchteten klinischen Verlaufsformen der *E. histolytica* Infektion. Interessanterweise tritt dieses Krankheitsbild vor allem bei Männern (>80%) auf. In diesem Zusammenhang wurde ein neues Tiermodell für Amöbenleberabszesse entwickelt, das eine ähnliche Geschlechterpräferenz aufweist wie beim Menschen und mit dem die Entstehung von Amöbenleberabszessen besser studiert werden kann (Hannelore Lotter).

Zwei Gruppen der Sektion Parasitologie haben sich der Forschung an Leishmanien gewidmet. Die **Arbeitsgruppe Clos** hat ein Regulatorprotein identifiziert, das die Proliferation und damit das Wachstum von Leishmanien beeinflusst. Darüber hinaus hat die Gruppe auf der Suche nach Mechanismen der Antibiotikaresistenz ein Gen aus Leishmanien isoliert, welches für ein bisher nicht bekanntes 299-kDa Protein kodiert. Dieses Protein ist offenbar beteiligt an der Resistenzentwicklung gegen Miltefosine, dem neuesten auf dem Markt befindlichen anti-Leishmanien-Medikament. Die **Arbeitsgruppe Wiese** konzentriert sich auf Untersuchungen zu Mitogen-Aktivierten-Protein (MAP)-Kinasen in *L. mexicana*. Diese Proteine haben eine wesentliche Kontrollfunktion für das Wachstum, die Differenzierung sowie bei der Flagellenentwicklung von Leishmanien. Das Genom von Leishmanien enthält zahlreiche Gene für MAP-Kinasen und deren Aktivatoren (MKK). Die aktuellen Untersuchungen gehen der Frage nach, ob und wenn ja welche dieser Kinasen als Zielstrukturen für die medikamentöse Behandlung von Leishmanien-Infektionen geeignet sind.

Die Erforschung der Malaria wird gegenwärtig in allen drei Sektionen des Instituts durchgeführt. Innerhalb der Sektion Parasitologie untersucht die **Abteilung Biochemie** (Rolf D. Walter) Stoffwechselwege des Parasiten, die sich wesentlich von denen des Menschen unterscheiden und damit vermutlich geeignete Zielstrukturen für Malariamedikamente darstellen. In diesem Zusammenhang wurden frühere Arbeiten zum Polyaminstoffwechsel von *P. falciparum* fortgeführt und viel versprechende Inhibitoren validiert (Kai Lüersen). Ein weiterer Ansatzpunkt für die Therapie der Malaria könnte die Stoffwechselwege für die Vitamine B1 und B6 sein, die kürzlich in Plasmodien entdeckt wurden (Carsten Wrenger). Detaillierte Analysen der einzigen Glutathion S-Transferase von *P. falciparum* zeigten, dass dieses Enzym sowohl mit Glutathion als auch mit dem für Parasiten toxischen Hemin interagiert (Eva Liebau).

Das Überleben intrazellulärer Parasiten ist abhängig von ihrer Fähigkeit, den programmierten Zelltod, die Apoptose von Wirtszellen, zu verhindern. Unter Verwendung des Maus-Malaria-Parasiten *P. berghei* als Modellsystem hat die **Arbeitsgruppe Heussler** die Überlebensstrategien von Plasmodien während der Entwicklung vom Sporozoiten zum Merozoiten in Hepatozyten untersucht. Dabei konnte sie zeigen, dass während der ersten beiden Tage der Infektion der Parasit die Wirtszelle vor Apoptose schützt, während anschließend die Apoptose eingeleitet wird und reife Merozoiten freigesetzt werden. Interessanterweise ergaben Untersuchungen insbesondere mit der Technik der Intravitalmikroskopie, dass die Freisetzung der Merozoiten nicht einfach durch Ruptur der Zelle geschieht, wie allgemein angenommen wurde. Vielmehr wird die infizierte Zelle veranlasst lange Fortsätze, so genannte Merosomen zu bilden, über die die Merozoiten die Endothelzellschicht passieren und direkt in den Blutstrom freigesetzt werden können.

Der Prozess der Zellinvasion durch Plasmodien umfasst eine Anzahl unterschiedlicher Proteine, die in spezialisierten Organellen lokalisiert sind. Der Transport und die Modifikation solcher Proteine sind Gegenstand der Untersuchung in der **Arbeitsgruppe Gilberger**. In diesen Zusammenhang hat die Gruppe den bis dahin nicht näher charakterisierten Golgi-Apparat von *P. falciparum* untersucht und erstmals eindeutig dargestellt. Diese membranhaltige Organelle stellt die zentrale Schaltstelle für die Sekretion und Modifikation von Proteinen in der Zelle dar.

Neben den rein protozoologischen Arbeiten wurden außerdem Feldstudien durchgeführt, um Vektoren zu charakterisieren, die für die Übertragung der Onchozerkose in Afrika verantwortlich sind (Andreas Krüger). Das Ziel dieser Arbeiten ist die Identifizierung von genetischen Markern zur besseren Unterscheidung von Mücken, die in der Lage sind *O. volvulus* auf den Menschen zu übertragen und solchen, denen diese Fähigkeit fehlt.

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Amoebic liver abscess: Why females do better than males

Department of Molecular Parasitology

Zusammenfassung

Der Amöbenleberabszess (ALA) ist eine Erkrankung, die durch die Infektion mit dem Darmparasiten *Entamoeba histolytica* hervorgerufen wird und die vor allem bei erwachsenen Männern (85%) und selten bei Frauen und Kindern auftritt. Wir haben kürzlich ein ALA-Tiermodell in immunkompetenten Mäusen etabliert, das einen ähnlichen Geschlechterunterschied wie beim Menschen aufweist. Nach intrahepatischer Applikation von *E. histolytica*-Trophozoiten zeigen weibliche Tiere eine schnelle Kontrolle des Infektion, während bei männlichen Tieren der Parasit über viele Tage nachweisbar ist und zu deutlicher Abszessbildung führt. Die Analyse der Immunantwort ergab, dass sich männliche und weibliche Mäuse hinsichtlich der frühen Zytokinantwort nach Amöbeninfektion der Leber unterscheiden. Die Ergebnisse lassen vermuten, dass im Gegensatz zu männlichen Tieren weibliche Tiere sehr schnell Makrophagen mit Hilfe von IFN-γ aktivieren können und somit frühzeitig die Amöben abtöten.

Summary

Amoebic liver abscess (ALA), a disease caused by infections with the enteric protozoan parasite *Entamoeba histolytica*, greatly predominates in males (>85%) but is rare in females. We recently established an ALA model in immunocompetent mice, which revealed a similar sexual dimorphism as found in humans. When intrahepatically challenged with *E. histolytica* trophozoites, female mice were able to rapidly control the infection whereas male mice harboured the parasite within the liver for at least 14 days and developed significant abscesses. Analysis of the immune response revealed that male and female mice differ in their early cytokine production in response to amoebic infection of the liver. The results suggest that females are able to rapidly activate macrophages via the IFN-γ-pathway, whereas development of ALA in males is due to inadequate activation of accumulated immune cells within the liver tissue.

Introduction

Amoebic liver abscess (ALA) is by far the most common extraintestinal manifestation of invasive amoebiasis as more than 99% of *E. histolytica*-induced abscesses are located within the liver. The disease is characterized by rapidly evolving, massive tissue destruction due to apoptotic and necrotic disintegration of hepatocytes. In contrast to intestinal amoebiasis, the occurrence of ALA is age- and sex-dependent. In children, the dominant clinical symptoms associated with *E. histolytica* infections are restricted to the gut whereas development of ALA is extremely rare. More than 95% of all ALA cases are found in adults. However, ALA greatly predominates in males (>85%). The risk for the development of ALA in females is more or less equally distributed between the different age groups with a slight increase in elder women above 60 years. In contrast, the risk for ALA in males increases after puberty with a peak incidence at approximately 40 years of age. This sexual dimorphism for the risk of ALA is independent from the prevalence of the parasite, which is usually higher in children and adult females than in adult males. Moreover, it appears to be independent of cultural or ethnic background as it has been observed in individuals in all parts of the world where amoebiasis is endemic as well as in travellers from countries where amoebiasis is not endemic.

Project Description and Results

Since humans are the only relevant host for *E. histolytica*, attempts to study host-related factors or the mechanisms underlying the observed ALA-associated gender differences have been hampered by the lack of suitable animal models. In recent years, several rodent species have been successfully used as models to study the development of ALA. Although amoebic liver lesions could be provoked by direct inoculation of *E. histolytica* trophozoites into the liver of rabbits, Syrian hamsters or Mongolian gerbils, these models revealed substantial limitations such as the lack of suitable tools for studying the immune response of infected animals and the fact that gender differences in response to amoebic infections were not observed.

Until recently it was thought that immunocompetent mice are incapable to develop ALA when infected with virulent *E. histolytica* trophozoites. However, nearly all of the previous studies have been performed in female mice. During our recent work on amoebiasis vaccine development, which requires the use of small laboratory animals, we observed that immunocompetent mice can be used as model organisms to study ALA. By serial liver passages of cultured *E. histolytica* trophozoites in gerbils and mice, we generated amoeba, which reproducibly induce ALA in C57BL/6 mice. Interestingly, all animals developed ALA, but the time-courses of abscess formation differed significantly between the genders. Female mice were able to clear the infection within 3 days, whereas in male mice the parasite could be recovered over a period of at least 14 days. Accordingly, male mice showed a prolonged recovery time from ALA. Immunohistology of abscesses revealed that polymorphonuclear leukocytes (PMNs) and macrophages were the dominant infiltrates, but in addition, γδ-T cells, NK cells and NKT cells were also present at early time points of abscess development, whereas conventional α,β-T cells appeared later when female mice had already

cleared the parasite. Interestingly, male and female mice differed in early cytokine production in response to amoeba infection. ELISPOT assays performed with spleen cells of infected animals revealed significantly higher numbers of IL4-producing cells in male mice but significant higher numbers of IFN-γ producing cells in female mice (Fig. 1). Early IFN-γ production and the presence of functional NKT cells was found to be important for the control of hepatic amoebiasis as application of an IFN-γ neutralizing monoclonal antibody (Fig. 2) or the use of NKT knock-out mice (Vα14iNKT, Jα $18^{-/-}$) dramatically increased the size of ALA in female mice. In addition, *E. histolytica* trophozoites could be re-isolated from liver abscesses of Jα $18^{-/-}$ mice on day seven post infection when wild type mice had already cleared the parasite. These data suggest that the sexual dimorphism in the control of ALA is due to gender specific differences in early cytokine production mediated at least in part by NKT-cells in response to *E. histolytica* infection of the liver.

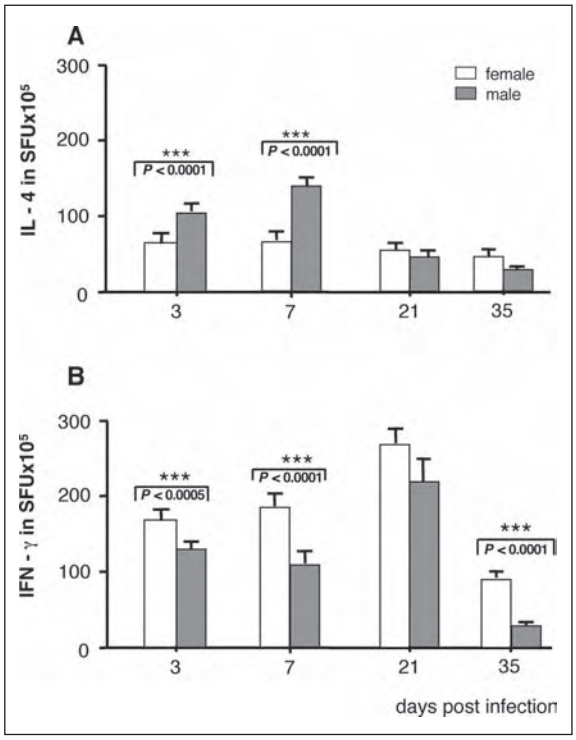

Figure 1: Time-course of IL-4 (A) and IFN-γ (B) production in male and female ALA mice. Cytokine-producing spleen cells were determined by ELISPOT assays. Spleen cells from male or female ALA mice were cultivated on antibody-coated plates for 24 h either in the presence of medium only or with the addition of anti-CD3. Plates were developed with the respective secondary antibody followed by the detection reagent. The number of cytokine-producing cells is expressed as spot forming units (SFU).

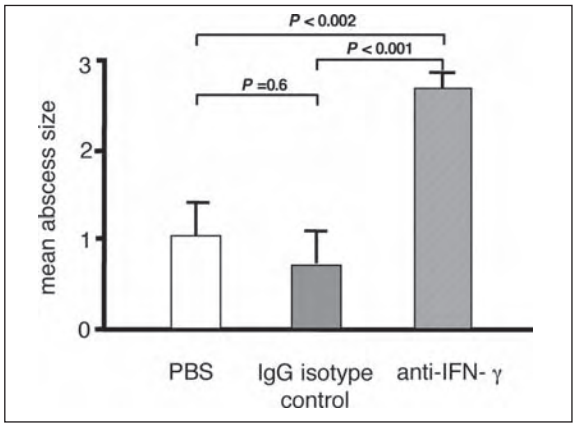

Figure 2: ALA in female mice after immunodepletion of IFN-γ. Ten female mice per group were immunized by intraperitoneal application of either 150 µl of phosphate buffered saline (PBS) or 500 µg of neutralizing monoclonal antibody against IFN-γ (anti- IFN-γ) or 500 µg of isotype-matched control antibody (IgG isotype control). One day later, animals were challenged by intrahepatic application of virulent *E. histolytica* trophozoites. The sizes of abscesses were scored on day 7 post infection.

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- Lotter H, Jacobs T, Gaworski I, Tannich E. **2006**. Sexual dimorphism in the control of amebic liver abscess in immunocompetent mice. Infect Immun 74:118-124
- Blessmann J, Khoa ND, Le Van A, Tannich E. **2006**. Ultrasound patterns and frequency of focal liver lesions after successful treatment of amebic liver abscess. Trop Med Int Health: in press

Funding

- DFG (German National Research Association)
- Volkswagen Stiftung

Cooperating Partners

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Investigators

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The *Entamoeba histolytica* genome

Department of Molecular Parasitology

Zusammenfassung

Die kürzlich erfolgte Aufklärung des Genoms von *Entamoeba histolytica* bedeutet einen großen Fortschritt für die Amöbenforschung. Die Analyse der Gensequenzen zeigte, dass sich *Entamoeba* durch eine Vielzahl besonderer metabolischer Anpassungen an das Leben im menschlichen Darm auszeichnet. Mitochondriale Stoffwechselwege konnten nicht nachgewiesen werden und viele Gene wurden offenbar durch lateralen Gentransfer von anaeroben Prokaryoten erworben.

Introduction

The protozoan *Entamoeba histolytica,* the causative agent of human amoebiasis, is endemic in most tropical and subtropical countries and is considered responsible for tens of millions of cases of dysentery and liver abscess each year. To fascilitate research on *E. histolytica,* the genome of this parasite has been sequenced by the Institute for Genomic Research (TIGR) in Rockville, Maryland, USA, and the Wellcome Trust Sanger Institute in Hinxton, Cambridge, UK, and was subsequently annotated by a large consortium of researchers from various laboratories throughout the world including the Bernhard Nocht Institute.

Project Description and Results

The *E. histolytica* genome sequence was generated by the whole-genome shotgun method. Genome analysis was carried out on a 12.5-fold coverage genome assembly consisting of about 24 Million base pairs. The 9,938 predicted genes average 1.17 kilobases in size and comprise 49% of the genome. One quarter of *E. histolytica* genes are predicted to contain introns, with 6% of genes containing multiple introns. The *E. histolytica* genome is highly repetitive. Ten percent of the genome is arranged in tandem arrays of one of the 25 different types of tRNA units, with one to five tRNA types per unit. No homologues could be identified for a third of predicted proteins from the public data bases.

To communicate with the environment *E. histolytica* has developed a remarkable number of genes coding for protein kinases. All of the seven major families of eukaryotic protein kinases are represented in the *E. histolytica* genome. Approximately 270 putative kinase genes were identified, including tyrosine kinases, tyrosine kinase-like protein kinases, and receptor serine/threonine kinases as well as about 100 protein phosphatases. The *E. histolytica* genome encodes putative seven-transmembrane receptors and G proteins. In general, G proteins consist of three subunits (alpha, beta, gamma), each represented by numerous family members in higher animals. Only one member of the alpha and the beta subunit family was identified in the *E. histolytica* genome. So far, no gene homologous to a gamma subunit was found. In addition *E. histolytica* contains several other proteins involved in signal transduction, like Ras proteins and MAP kinases.

E. histolytica trophozoites usually reside in the human gut, which constitutes an anaerobic or microaerophilic environment. However, during tissue invasion, the amoebae are exposed to an increased oxygen pressure and have to eliminate toxic metabolites such as reactive oxygen or nitrogen species (ROS/RNS). Analysis of the *E. histolytica* genome revealed only a single gene coding for an iron-containing superoxide dismutase (FeSOD), an antioxidant enzyme that belongs to the first line of oxidative defense. It catalyses the dismutation of superoxide radical anions to form H_2O_2 and O_2. *Entamoeba histolytica* lacks the tripeptide glutathione as well as all antioxidant enzymes that use glutathione as cofactor such as glutathione-dependent peroxidase and glutathione reductase. In addition, genes for catalases and peroxidases are absent. However, other genes coding for proteins involved in detoxification of H_2O_2, including one with homology to rubrerythrin are present. Another group of H_2O_2-detoxifying proteins present in *E. histolytica* are peroxiredoxins. They are able to reduce H_2O_2 as well as peroxynitrite with the use of electrons provided by thiols. Reactions catalysed by peroxiredoxins are dependent on the presence of physiological thiols like thioredoxin. Thioredoxins are small proteins involved in thiol-redox processes. They contain two redox-active site cysteine residues which are kept in the reduced state by the enzyme thioredoxin reductase, which catalyses the reduction of oxidised thioredoxin by NADPH using FAD and its redox-active disulphide. Five genes coding for thioredoxins and two genes with homology to thioredoxin reductases were found in the *E. histolytica* genome. In addition, four other gene families were identified coding for flavoproteins. One of these families includes 4 members with identity to A-type flavoproteins. A-type flavoproteins belong to a large family of enzymes, widespread among anaerobic prokaryotes. The N-terminal part of the A-type flavoprotein forms a metallo-beta-lactamase-like domain, containing a non-heme di-iron site, whereas the C-terminal part constitutes a flavodoxin-like domain, containing on FMN moiety. These enzymes have significant nitric oxide reductase activity.

E. histolytica lacks mitochondria and as a consequence a mitochondrial genome. The parasite drives its energy from glycolysis and fermentation. Several enzymes form these pathways descended by lateral gene transfer from prokaryotes. It has been estimated that at least 96 genes have been incorporated into the *E. histolytica* genome by lateral transfer from prokaryotes.

E. histolytica is characterized by its extraordinary capacity to invade and destroy human tissues. The main histolytic activity has been attributed to cysteine proteinases. This class of enzymes is considered to play a major role for the pathogenicity of *E. histolytica*. Homology searches based on the conservation of active site regions revealed that the *E. histolytica* genome contains a multitude of at least 44 genes coding for cysteine proteinases. Of these, the vast majority is structurally related to the C1 papain superfamily, whereas a few others are more similar to family C2 (calpain-like cysteine proteinases), C19 (ubiquitinyl hydrolase), C54 (autophagin), and C65 (otubain), respectively. Phylogenetic analyses of the 36 C1-family members revealed that they represent 3 distinct clades (A, B, C), each consisting of 12, 11 and 13 members, respectively (Fig. 1). EhCP-A and EhCP-B family members are classical pre-pro enzymes with an overall cathepsin L-like structure. Interestingly, biochemical studies with purified EhCP-A molecules indicated a cathepsin B-like substrate specificity. EhCP-A and EhCP-B subfamilies differ in length of the pro regions as well as of the catalytic domains and have specific sequence motifs within the N-terminal regions of the mature enzymes. Moreover, none of the EhCP-A members but 10 out of 11 EhCP-B sequences contain hydrophobic stretches near or at the N-terminus, some of them are predicted to constitute transmembrane helices (TMH) or GPI-attachment moieties. Instead of a pro-region, EhCP-C members contain a hydrophobic region near the N-terminus, which is predicted to form a TMH. In addition to cysteine proteinases, analysis of the *E. histolytica* genome indicates the presence of at least 4 members of the aspartate-, 6 members of the serine-, and 23 members of the metalloproteinase family. Several of them contain putative TMHs. So far, the function of none of these enzymes has been characterized. In summary, the *Entamoeba* genome contains a considerable number of peptidase genes. Elucidation of the precise role of each of the various enzymes appears to be a major challenge but may help to understand the mechanism(s) of virulence and other unique properties of this protozoan parasite.

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- Willhoeft U, Tannich E. **1999**. The electrophoretic karyotype of *Entamoeba histolytica*. Mol Biochem Parasitol, 99, 41-53
- Willhoeft U, Campos-Góngora E, Touzni S, Bruchhaus I, Tannich E. **2001**. Introns of *Entamoeba histolytica* and *Entamoeba dispar*. Protist, 152, 149-256.
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Funding

- DFG (German National Research Association)
- Evangelisches Studienwerk e.V.

Cooperating Partners

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- Ute Willhoeft
- Egbert Tannich

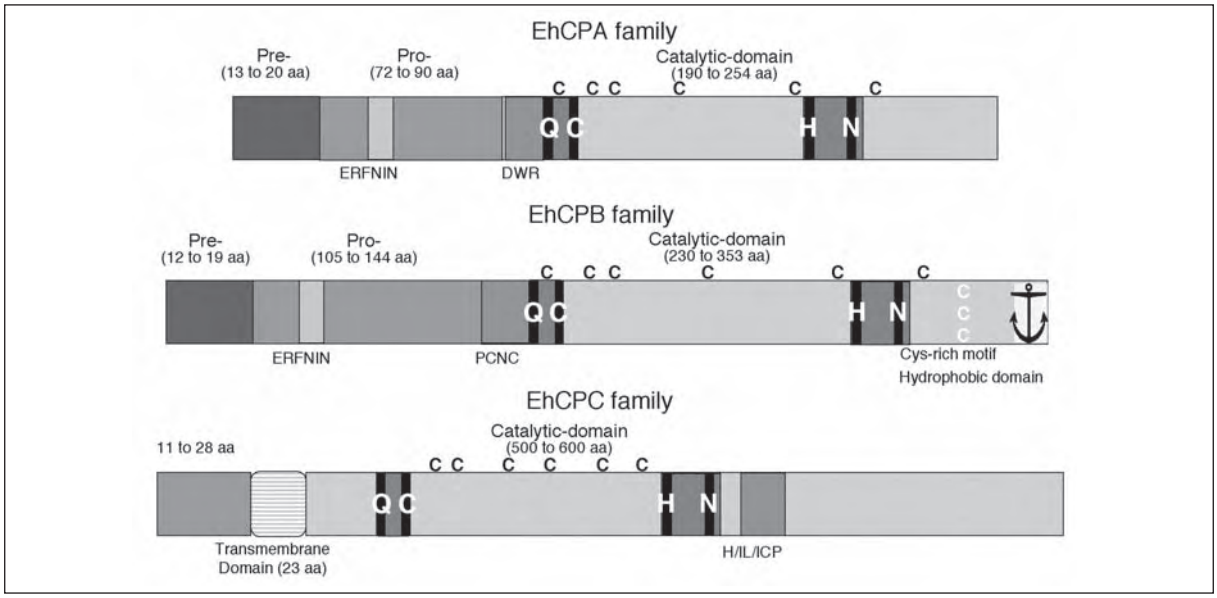

Figure 1: Scheme of the primary structure of the three cathepsin-L-like cysteine proteinase families of *E. histolytica*

Evolution of the *Simulium damnosum* complex

Department of Molecular Parasitology

Zusammenfassung

Die molekulare Phylogenie und Evolution des *Simulium damnosum* Komplexes, einschließlich der Überträger des Humanparasiten *Onchocerca volvulus* aus weiten Teilen Afrikas wurde untersucht und mit Ergebnissen früherer zytogenetischer Analysen verglichen. DNA-Sequenzvergleiche ergaben, dass der Komplex aus einem mehr ost- und einem eher westafrikanischen Zweig besteht. Dabei bilden *S. pandanophilum* (Uganda) und *S. mengense* (Kamerun) jedoch einen basalen, zentralafrikanischen Zweig und werden somit auch als zytogenetisch ursprüngliche Arten angesehen. Außerdem implizieren die Ergebnisse überraschend frühe Artentstehungsprozesse in der Zeit vor 2 Mio. Jahren. Dieser Zeitrahmen korrespondiert mit einschneidenden Änderungen des afrikanischen Klimas und der Vegetation in den letzten 3 Mio. Jahren.

Introduction

In Africa, blackflies of the *Simulium damnosum* complex are the main vectors of the filarial nematode *Onchocerca volvulus*, the cause of human onchocerciasis. Only some of the about 50 constituent sibling species of the complex are anthropophilic and transmit the parasite. This fact not only complicates considerably the disease epidemiology, but also makes the complex the record-holder for the highest number of siblings in animals. Sibling species represent a controversial issue in taxonomy. According to the general species concept, their status relies on the assumption that they are reproductively isolated. This, however, is hardly demonstrable due to the reluctance of blackflies to mate in captivity. On the other hand, the remarkable diversity within a – formerly considered one – species naturally provokes zoogeographic, phylogenetic and evolutionary questions. Phylogenetics of the *S. damnosum* complex so far mostly relied on cytotaxonomic studies which, by means of chromosome inversion differences, revealed an un-rooted cytophylogeny. Recently, this situation could be improved by re-examining new samples cytotaxonomically and by employing molecular techniques.

Project Description and Results

The cytological analyses of three geographically isolated non-vector species, *S. mengense* (Cameroon), *S. pandanophilum* (Uganda) and *S. damnosum* 'Kibwezi' (Tanzania), revealed that some, apparently primitive chromosome arrangements could be derived from each other (Fig. 1). This and the disjunct geographic distribution led to the assumption that the three species may represent distantly related relic taxa.

In order to test the cytophylogenetic hypotheses and to provide further evolutionary aspects, the molecular phylogeny of a broad selection of specimens of *S. damnosum* s.l. from various parts of Africa and the Yemen was investigated. Samples were analysed for portions of the mitochondrial (mt) 16s ribosomal RNA and NADH dehydrogenase subunit 4 (ND4) genes, and sequence data of the internal transcribed spacer 2 (ITS2) of the nuclear ribosomal DNA were used as phylogenetic markers for the first time. Initially conducted mtDNA sequence analyses (16s, ND4) produced some inconsistencies with regard to cytophylogeny and biogeography of certain taxa and disagreed, for instance, to the old relationship of the relic taxa. In an attempt to overcome these problems the ITS2 was analysed. Again, there arose inconsistencies, now between the mitochondrial and the nuclear trees, with the latter being more congruent with cytological data. These discrepancies could be due to mitochondrial gene flow within certain geographical areas. However, by inclusion of non-*damnosum* outgroup specimens and by translation of the molecular tree topology into the chromosomal relationships it was now possible to estimate the first rooted cytophylogenetic tree of the complex (Fig. 2). *Simulium mengense* and *S. pandanophilum* constitute the oldest branch, and 'Kibwezi' together with two Ethiopian taxa appear as a sister clade of a West African branch (which includes most vectors of the complex), as opposed to another major clade comprising the remaining eastern and southern African taxa (only three of which are vectors). Based on molecular as well as cytological and morphological evidence, two new species of the East African branch, namely *S. kipengere* and *S. plumbeum*, were described.

Since *S. pandanophilum* and *S. mengense* are confined to core areas for old forest endemics, then the Congo forest basin may be regarded as the "centre of speciation" of the complex, whereas the greatest diversity of lineages can be found in the highlands between Ethiopia, Uganda and Tanzania. This triangle is therefore suggested to be the "centre of greatest diversity". Another forest lineage that is found in the western parts of the Congo basin is *S. squamosum*, which appears to be basal at least within the western branch of the complex. Consequently, the numerous non-forest taxa, i.e. those found in savanna woodlands or 'mosaic' habitats, represent younger lineages. Indeed, this could explain the swarm-like cluster within some lineages (Fig. 2). On the other hand, a sylvatic origin of vectors correlates with the observed lower pathogenicity of forest strains of *O. volvulus*, which are better adapted to humans than the younger savanna strains. The sequence data were also utilized to estimate the divergence times of the major lineages of the complex. The root of the

complex surprisingly dates back to some 2 to 3 million years (Myr), followed by the appearance of the West and East African lineages about 1.5 Myr ago and further splits near 1 Myr ago.

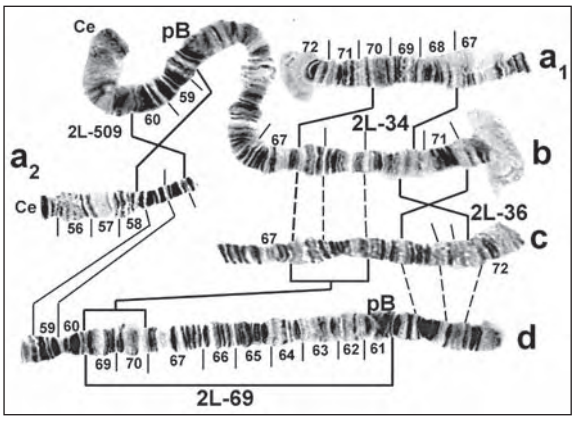

Figure 1: Long arms of chromosome 2.
(a) standard sequence, *S. kilibanum*;
(b) cytoform 'Kibwezi'; (c) *S. mengense*;
(d) *S. pandanophilum*

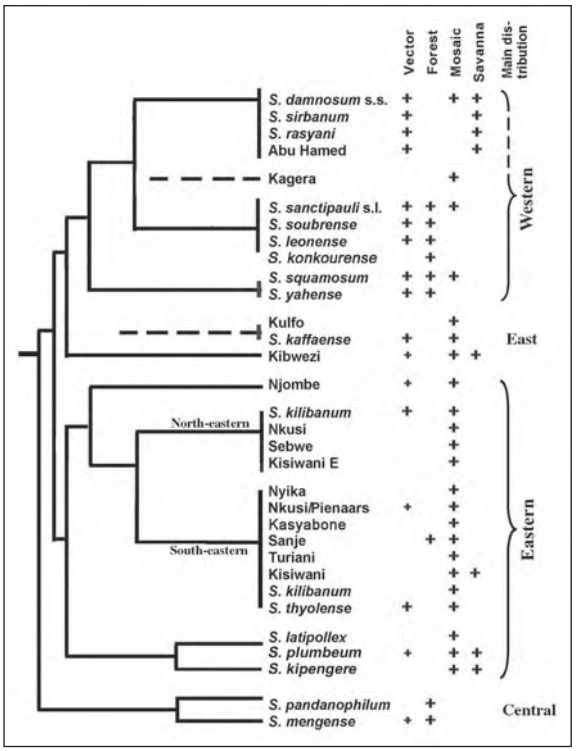

Figure 2: Revised and rooted phylogeny of the *S. damnosum* complex, with vector status and ecological characteristics. Lower case vector symbols demarcate either man-biting only without transmission, or status for certain populations only.

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Cooperating Partners

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Polyamine synthesis in the human malaria parasite *Plasmodium falciparum:* Assessment of enzyme inhibitors as drug candidates

Department of Biochemical Parasitology

Zusammenfassung

Polyamine sind essentiell für Zellvermehrung und Differenzierung und somit ein Angriffsziel für die Therapie von Tumoren sowie von Infektionen mit schnell proliferierenden Parasiten. Bei dem Malariaerreger *Plasmodium falciparum* haben wir nachgewiesen, dass Ornithin- und S-Adenosylmethionin-Decarboxylase, die regulatorischen Enzyme in der Polyaminsynthese, von einem gemeinsamen Gen kodiert werden und als bifunktionelles Protein vorkommen. Die Polyaminsynthese wird durch diesen ungewöhnlichen Enzymkomplex, der möglicherweise mit der Spermidin-Synthase assoziiert ist, kontrolliert. Struktur, Funktion und zellphysiologische Bedeutung dieser drei Enzyme, die bei Plasmodien ausschließlich für die Polyaminsynthese verantwortlich sind, wurden analysiert, insbesondere wurde ihre Bedeutung für eine rationale Medikamentenentwicklung untersucht.

Introduction

Treatment of Malaria is being compromised by spreading resistance against the commonly used antimalarial drugs. Therefore, the evaluation of new drug targets and the identification of compounds with plasmodicidal activity are of urgent need. During their erythrocytic schizogony *P. falciparum* proliferate rapidly within their host cells, leading to 12-18 new merozoites every 48 h. It has been shown for many organisms that growth and differentiation processes depend on adequate intracellular concentrations of the polyamines putrescine, spermidine and spermine. As a consequence, depletion of cellular polyamine levels has an anti-proliferative effect on cells, including *P. falciparum*.

The polyamine synthesis pathway contains two regulatory steps, catalysed by ornithine decarboxylase (ODC) and *S*-adenosylmethionine decarboxylase (AdoMetDC). ODC converts the amino acid ornithine into putrescine. AdoMetDC generates decarboxylated *S*-adenosylmethionine (dcAdoMet) that is required as aminopropyl group donor by spermidine and spermine synthase to form spermidine and spermine, respectively. Usually, ODC and AdoMetDC represent two separate proteins encoded by two individual genes. In *P. falciparum*, however, both enzymes are located on a single open reading frame, which encodes a unique bifunctional ODC/AdoMetDC protein. Although it has been shown that – despite of this unusual organisation – both domains act independently, *P. falciparum* ODC and AdoMetDC exhibit specific regulatory features that are distinct from the monofunctional host enzymes, which may offer possibilities for the design of new chemotherapies against malaria.

Project Description and Results

The intraerythrocytic development of *P. falciparum* correlates with increasing levels of the polyamines putrescine, spermidine and spermine in the infected red blood cells (RBC) and compartimental analyses revealed that the majority is associated with the parasite (Fig. 1 and Table 1).

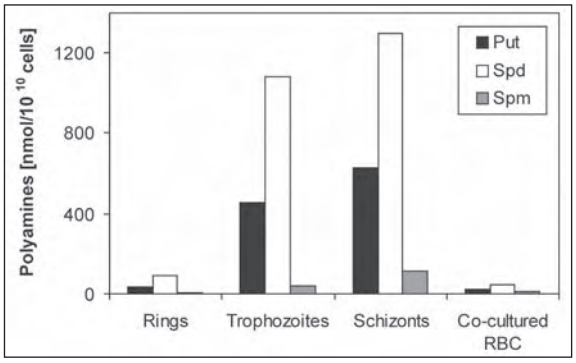

Figure 1: Stage-specific polyamine content of *P. falciparum*-infected red blood cells

Table 1: Compartimental analysis of polyamine distribution in *P. falciparum*-infected RBCs

	Polyamines [nmol 10^{10} cells^{-1}]		
	Putrescine	Spermidine	Spermine
Parasite/ host unit	164.6 ± 69.8	865.9 ± 342.5	45.7 ± 21.5
Parasite compartment	104.7 ± 54.1	686.8 ± 299.4	34.0 ± 19.3
Host cell compartment	41.9 ± 9.6	140.4 ± 37.0	11.9 ± 6.8

Since depletion of cellular polyamines is a promising strategy to inhibit parasite proliferation, new inhibitors of polyamine synthesis were tested for their antimalarial activities. The ODC inhibitor 3-aminooxy-1-aminopropane (APA) and its derivatives CGP 52622A and CGP 54169A (Fig. 2) as well as the AdoMetDC inhibitors CGP 40215A and CGP 48664A potently affected the bifunctional *P. falciparum* ODC/AdoMetDC with K_i values in the low nanomolar and low micromolar range, respectively. Furthermore, the agents were examined for their *in vitro* plasmodicidal activity in 48 h incubation assays. APA, CGP 52622A, CGP 54169A and CGP 40215A were most effective with IC_{50} values below 3 µM (Table 2).

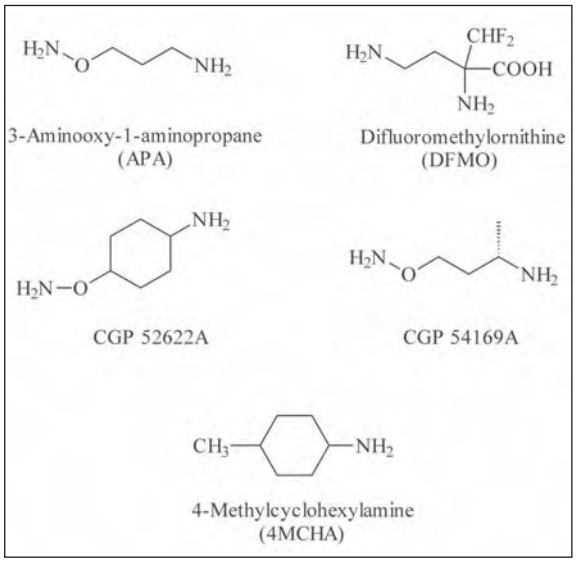

Figure 2: Structure of ODC and spermidine synthase inhibitors

Table 2: The effect of ODC inhibitors on enzyme activities and the survival rate of cultured *P. falciparum* and murine B-cell lymphoma A20/J2 cells

	K_i value	IC_{50} value in *P. falciparum* culture	IC_{50} value in mammalian cell culture
ODC inhibitor	[nM]	[µM]	[µM]
APA	2.7 ± 0.5	1.0 ± 0.3	12.8 ± 3.6
CGP 54169A	7.9 ± 2.1	2.0 ± 0.3	40.8 ± 16.3
CGP 52622A	20.4 ± 8.1	2.7 ± 0.2	12.2 ± 3.2
DFMO	87600 ± 14300	1250 ± 420	n.d.
AdoMetDC inhib.			
CGP 40215A	0.8 ± 0.2	1.8 ± 0.4	74.4 ± 3.8
CGP 48664A	3.0 ± 0.9	8.8 ± 1.7	0.18 ± 0.07

While the effects of the ODC inhibitors were completely abolished by the addition of putrescine, growth inhibition by the AdoMetDC inhibitor CGP 40215A could not be antagonized by putrescine or spermidine. Moreover, CGP 40215A did not affect the cellular polyamine levels, indicating a mechanism of action against *P. falciparum* independent of the polyamine synthesis. In contrast, the ODC inhibitors led to decreased cellular putrescine and spermidine levels in *P. falciparum* supporting that they exert their antimalarial activity by inhibition of the bifunctional ODC/AdoMetDC. These ODC inhibitors are notably more potent than the classical ODC inhibitor and sleeping sickness drug DFMO against *P. falciparum* in vitro, and it is certainly worthwhile to analyse the antimalarial activities of APA and derivatives in animal model systems.

Further studies revealed that *P. falciparum* lack a spermine synthase, however, in contrast to its mammalian counterpart, the spermidine synthase can replace to some extent putrescine by spermidine as the aminopropyl acceptor. Hence, the plasmodial enzyme has the capacity to catalyse the formation of spermine that is found in small amounts in the erythrocytic stages of the parasite. Among the spermidine synthase inhibitors tested against *P. falciparum* spermidine synthase, *trans*-4-methylcyclohexylamine (4MCHA, Fig. 2) was found to be most potent with a K_i value of 0.18 µM. In contrast to the situation in mammals, where inhibition of spermidine synthase has no or only little effect on cell proliferation, 4MCHA was an efficient inhibitor of *P. falciparum* cell growth *in vitro* with an IC_{50} of 35 µM, indicating that *P. falciparum* spermidine synthase might represent a promising drug target.

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Funding

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Vitamin B1 and B6 biosyntheses in the human malaria parasite *Plasmodium falciparum*

Department of Biochemical Parasitology

Zusammenfassung

Pyridoxalphosphat (PLP) und Thiaminpyrophosphat (TPP) sind Cofaktoren essentieller Enzyme, die in allen Organismen vorkommen. Die Biosynthese dieser Cofaktoren ist beschrieben von Bakterien, Pilzen und Pflanzen, fehlt hingegen beim Menschen und anderen Vertebraten, die auf eine Aufnahme dieser Cofaktoren in Form der Vorstufen Vitamin B1 und B6 mit der Nahrung angewiesen sind. Aufbauend auf Hinweisen aus dem *Plasmodium falciparum*-Genomprojekt wurde das Vorkommen der *de novo*-Synthesen dieser beiden Vitamine im humanen Malariaerreger analysiert. Bekanntermaßen stellen Vitaminsynthesen ausgezeichnete Angriffspunkte für die Chemotherapie der Malaria dar, weil solche Stoffwechselwege parasitenspezifisch sind, so dass zu entwickelnde Inhibitoren nicht mit dem Stoffwechsel des Patienten interagieren. Um die Eignung der *de novo*-Synthesen der Cofaktoren PLP und TPP für eine rationale Medikamentenentwicklung zu bewerten, sollten nicht nur die beteiligten Syntheseenzyme charakterisiert, sondern auch die essentielle Bedeutung dieser Synthesen für das Überleben der Plasmodien nachgewiesen werden.

Project Description and Results

Aim of the project is to assess the vitamin B1 and B6 biosynthesis in the malaria parasite *Plasmodium falciparum* as a target for the design of new chemotherapeutic approaches for malaria therapy, urgently needed to overcome the worldwide spread of drug resistance. Despite the essential and crucial role of thiamine pyrophosphate and pyridoxal phosphate as cofactors of numerous key enzymes in the metabolism of parasite and host, their metabolism in the pathogenous agents is still a neglected area of research. Comparative genome analyses propose that the human malaria parasite possesses its own vitamin B1 and B6 biosyntheses, thereby presenting an unique parasite specific drug target. During the time course of this report, the biosyntheses of both vitamins were clearly demonstrated in *P. falciparum*. Genes/enzymes identified by comparative genome analysis to be involved in these pathways were recombinantly expressed and functionally characterized.

Vitamin B6 synthesis: Mammalian cells are unable to synthesise vitamin B6 *de novo*, whereas plants, fungi and bacteria possess a functional vitamin B6 synthesis pathway. *P. falciparum* expresses the proteins Pdx1 and Pdx2, corresponding to the yeast enzymes SNZ1 and SNO1, which are essential for the vitamin B6 biosynthesis (Fig. 1).

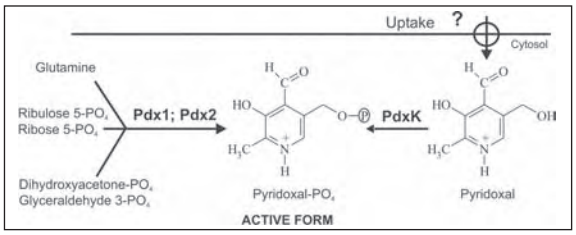

Figure 1: Vitamin B6 biosynthesis in *P. falciparum*

An involvement of *Pf*Pdx1 and *Pf*Pdx2 in the *de novo* synthesis of vitamin B6 was shown by complementation of pyridoxine auxotroph yeast cells. Both plasmodial proteins act together in the glutaminase activity. Incubating of the parasites with methylene blue revealed by Northern blot analysis an elevated transcriptional level of *Pf*Pdx1 and *Pf*Pdx2, suggesting a participation of these proteins in the defences against singlet oxygen. To be an active cofactor vitamin B6 has to be phosphorylated by the pyridoxine kinase (PdxK). The plasmodial PdxK has been recombinantly expressed and analysed for its kinetic parameters. All three enzymes expose stage specific transcription pattern within the trophozoite stage that guarantees the concurrent expression of Pdx1, Pdx2 and PdxK for the indispensable provision of vitamin B6. The occurrence of the vitamin B6 *de novo* synthesis pathway displays a potential new drug target, however, it awaits for demonstration by gene knockout experiments that its own B6 synthesis is essential for survival and growth of the human malaria parasite *P. falciparum*.

Vitamin B1 synthesis: Thiamine pyrophosphate is the essential cofactor for several key enzymes within carbohydrate metabolism. In *P. falciparum* the B1 biosynthesis pathway consists of the three enzymes 5-(2-hydroxy-ethyl)-4-methylthiazole kinase (ThiM), 4-amino-5-hydroxymethyl-2-methylpyrimidine kinase (ThiD) and thiamine phosphate synthase (ThiE) (Fig. 2).

The recombinant *Pf*ThiM and *Pf*ThiD proteins were biochemically characterized. Further, the ability of *Pf*ThiD and *Pf*ThiE for a participation in vitamin B1 biosynthesis was analysed by a complementation assay with *thiD* and *thiE* negative *E. coli* mutants, respectively (Fig. 3).

All three enzymes are expressed throughout the developmental blood stages as shown by Northern blotting, which indicates the occurrence of the vitamin B1 biosynthesis enzymes. However, cultivation of the parasite in minimal medium demonstrated a dependency for the provision of HMP or thiamine (Fig. 4). These results demonstrate that the human malaria parasite *P. falciparum* possesses an active vitamin B1 biosynthesis, which depends on external provision of thiamine precursors.

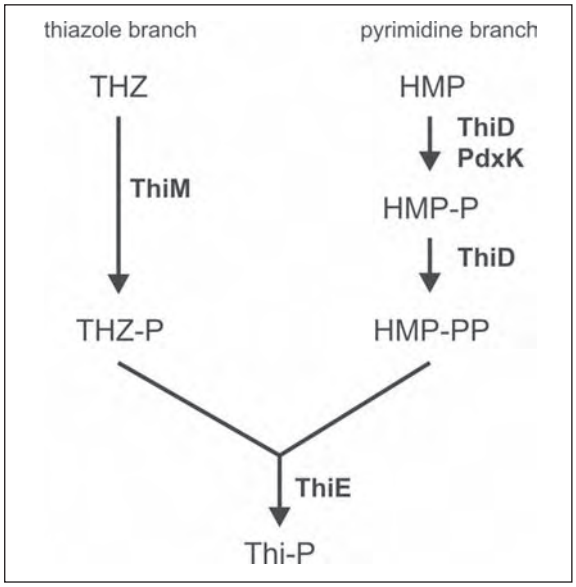

Figure 2: Vitamin B1 biosynthesis in *P. falciparum* is divided in two branches. 5-(2-Hydroxyethyl)-4-methylthiazole (THZ) is proposed to be synthesised *de novo* and phosphorylated to THZ-P by THZ-kinase (ThiM). In the other branch 4-amino-5-hydroxymethyl-2-methylpyrimidine (HMP) is phosphorylated to HMP-P by either the pyridoxine kinase (PdxK) or the HMP-(P)-kinase (ThiD). Subsequently HMP-P is phosphorylated to HMP-PP by the HMP-(P)-kinase. THZ-P and HMP-PP are merged to thiamine phosphate (Thi-P) in a reaction catalysed by thiamine synthase (ThiE).

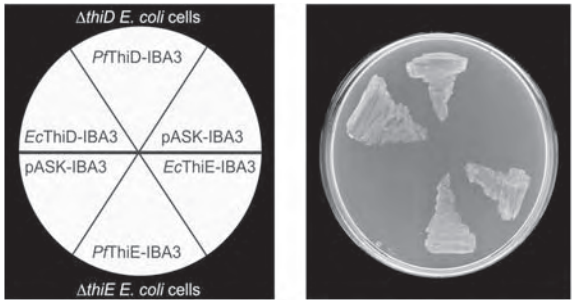

Figure 3: Complementation of Δ*thiD* and Δ*thiE* deficient *E. coli* cells by *Pf*ThiD and *Pf*ThiE. (A) Schematic scheme of the complementation assay. (B) The Δ*thiD* deficient *E. coli* cells were transformed with the *Ec*ThiD-IBA3 and *Pf*ThiD-IBA3 expression constructs carrying the open reading frames for either the *E. coli* or the plasmodial *thiD*, respectively. As a control, the empty expression vector pASK-IBA3 was also transformed into the bacterial mutant. Growth of the transformed Δ*thiD* mutants was analysed on M9 minimal medium agar without thiamine supplementation. Analogue to the ThiD complementation assay Δ*thiE E. coli* mutants were transformed with the *Ec*ThiE-IBA3 and *Pf*ThiE2-IBA3 and the empty pASK-IBA3 vector.

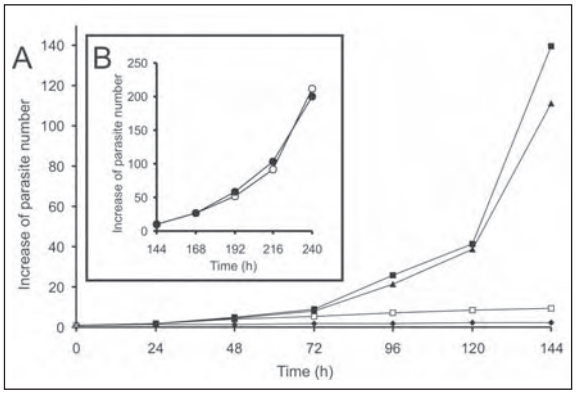

Figure 4: Growth analysis of cultured *P. falciparum*. (A) *P. falciparum* was cultured in minimal RPMI 1640 medium with (■) and without (□) supplementation of thiamine. Additionally, the parasites were incubated in the presence of THZ (♦) or THZ + HMP (▲). (B) To those parasites, which had been maintained for 144 h in minimal RPMI 1640 medium without (□) thiamine supplementation, HMP (○) and thiamine (●) have been added separately and cultivated for additional 96 h.

Selected Publications

- Wrenger C, Eschbach ME, Müller IB, Warnecke D, Walter RD. **2005**. Analysis of the vitamin B6 biosynthesis pathway in the human malaria parasite *Plasmodium falciparum*. J Biol Chem 280:5242-5248
- Wrenger C, Eschbach ML, Müller IB, Laun NP, Begley TP, Walter RD. **2006**. Vitamin B1 synthesis in the human malaria parasite *Plasmodium falciparum*. Biol Chem: 387: 41-51

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Characterization of a prokaryotic-type protease found in *Leishmania spp.*

Research Group Clos (Leishmaniasis I)

Zusammenfassung

Wir untersuchen einen putativen Protease-Komplex aus *Leishmania*, der einer bakteriellen Protease, HSL-VU, entspricht und zusätzlich zu dem allen Eukaryonten gemeinsamen 20S-Proteasom existiert. Nach unseren Erkenntnissen ist die *Leishmania* HSL-V-Protease hauptsächlich am apikalen Ende der Zelle, nahe der Geißeltasche, lokalisiert und scheint eine essenzielle, nicht redundante Funktion zu erfüllen. Daher soll die Eignung von HSL-VU als therapeutische Zielstruktur überprüft werden.

Introduction

We have characterised a putative protease complex from *Leishmania*, highly homologous to the bacterial HSL-VU proteases, which exists in addition to the usual eukaryotic 20S proteasome. We find that HSL-V localises predominantly to the apical end, close to the flagellar pocket and that its function is probably essential and non-redundant. Therefore, we plan to evaluate the potential of HSL-VU as therapeutic target structure.

Project Description and Results

Energy-dependant degradation of proteins is of vital importance to all living cells. The proteases involved play pivotal roles in the quality control of proteins, the steady state level control, the cellular stress response, and antigen presentation, among others.

In eukaryotes, the 20S proteasome structure is responsible for the degradation of proteins marked for destruction by conjugation with ubiquitine polypeptides. The proteasomal core structure consists of seven distinct alpha and seven distinct beta subunits that are expressed from sets of related genes.

Prokaryotes possess the related HSL-VU protease complex which consists of two hexameric rings of HSL-V and and one ring of HSL-U subunits, respectively. *HSL-V* and *HSL-U* were first identified as heat shock inducible genes, and they have a moderate impact on stress tolerance in Gram-positive bacteria.

HSL-V and *HSL-U* genes are absent from mammalian genomes and most other eukaryotes, and until recently, it was assumed that the presence of 20S proteasome and HSL-VU was mutually exclusive.

In the framework of the TriTryp Genome Projects (*T. brucei, T. cruzi*, and *L. major*), the existence of *HSL-V* and *HSL-U* related genes was discovered in the genomes of kinetoplastid protozoa. In addition, *HSL-V* and *HSL-U* genes were found in the genomes of *Plasmodium spp.* and in *Eimeria tenella*. They are notably absent, however, from *Entamoeba histolytica* and *Dictostelium discoidum* genomes. All of these protozoa contain *bona fide* genes for alpha and beta proteasome subunits in addition to the *HSL-V* genes. This raises the question whether the *HSL-V and HSL-U* genes in protozoa are redundant in function to the 20S proteasome structure or whether they perform specific functions. Preliminary phylogenetic analyses (not shown) argue against lateral gene transfer as a source for these genes since all protozoan *HSL-U* genes cluster separately from their eubacterial counterparts, even from orders as distant as the kinetoplastida and apicomplexa.

We expressed *L. infantum* HSL-V in *E. coli* and used the recombinantly expressed protein to raise polyclonal antibodies. Western Blot analyses revealed that HSL-V expression in *Leishmania* is not heat-inducible as it is in bacteria. Immune fluorescence imaging revealed a highly restricted localisation, apical relative to the nucleus (Figure 1). This assessment was corroborated by immunogold electron microscopy (Figure 2). HSL-V was found to localise to one face of the flagellar pocket, the parasite's main interface with its environment.

In spite of the presence of HSL-V and HSL-U, *L. donovani* was highly sensitive to specific proteasome subunit inhibitors such as clasto-lactacystin and epoxomycin (not shown), indicating that HSL-VU cannot complement for the inhibition of the 20S proteasome.

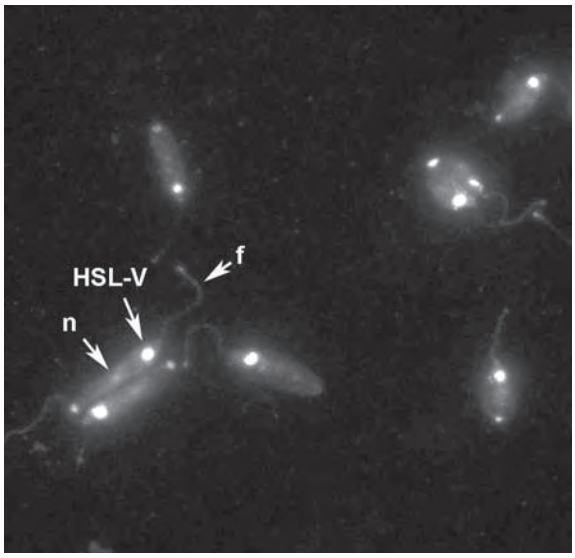

Figure 1: Immune fluorescence of *L. major* promastigotes, using anti-HSL-V antibody. Nucleus (n) and flagellum (f) are indicated.

The *L. major HSL-V* gene was targeted for replacement by homologous recombination to assess the impact of a lack of HSL-V on viability and virulence. Heterozygous replacement mutants were obtained, showing reduced growth *in vitro*. Subsequent attempts to replace the second allele of *HSL-V* failed repeatedly, and we aim at verifying that HSL-V is indeed essential for proliferation of *L. major in vitro*.

Under the assumption that *HSL-V* is an essential gene present in at least three genera of human-pathogenic protozoa, we have established simultaneous expression of *Leishmania* HSL-V and HSL-U in *E. coli* to

- obtain structural data of a HSL-VU complex for *in silico* screening of potential inhibitor molecules
- establish an *in vitro* activity assay to screen for inhibitors.

HSL-VU proteases have not been investigated as targets for therapeutic intervention. However, a distinct, essential role in protozoa and the complete lack of these proteins from humans would argue strongly in favour of exploring the potential of HSL-VU inhibitors.

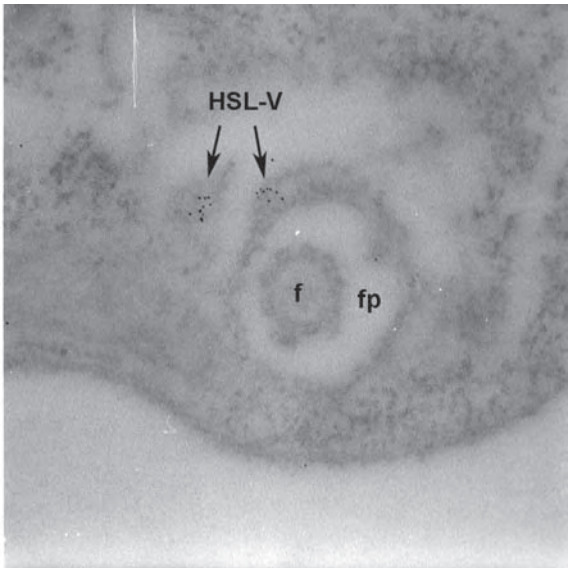

Figure 2: Immunogold electron microscopy using anti-HSL-V antibody and anti-mouse immunogold particles. The positions of flagellum (f) and flagellar pocket (fp) are indicated.

Investigators

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Signal transduction in *Leishmania:* Deletion analysis of parasite protein kinases

Research Group Wiese (Leishmaniasis II)

Zusammenfassung

Parasitische Protozoen der Gattung *Leishmania* (Kinetoplastida, Trypanosomatidae) durchlaufen einen digenetischen Lebenszyklus mit zwei morphologisch und biochemisch klar unterscheidbaren Lebensstadien. Differenzierung und Vermehrung des Parasiten werden durch Proteinkinasen reguliert. Gegen *Leishmania*-Kinasen gerichtete, spezifische Hemmstoffe sind daher ideale Wirkstoffe, die die Anpassung des Erregers an den Wirt behindern oder seine Vermehrung unterbinden. Durch Deletionsanalyse konnten wir zeigen, dass die MAP Kinase LmxMPK4 essentiell für den Parasiten ist und daher ein viel versprechendes Ziel zur Medikamentenentwicklung darstellt. Die MAP Kinase LmxMPK9 ist an der Regulation der Flagellenlänge beteiligt. Schließlich nimmt die MAP Kinase Kinase LmxPK4 Einfluss auf die Virulenz des Parasiten.

Introduction

The parasitic protozoon *Leishmania* causes different forms of leishmaniasis: cutaneous Leishmaniasis is characterized by skin lesions that are often self-healing and lead to immunity to re-infection; diffuse cutaneous leishmaniasis with disseminated lesions; mucocutaneous disease affecting the mucous membranes of the nose, mouth and throat; and visceral leishmaniasis, the most severe form of the disease, characterized by irregular fever, pancytopenia, hepatosplenomegaly, hypergammaglobulinaemia, and anaemia. Worldwide, 12 million cases of Leishmaniasis have been estimated, with 1.5 – 2 million new cases occurring annually (World Health Organization 1998). The disease is endemic in 88 countries on four continents with a total of 350 million people at risk of infection and is prevalent wherever mammalian reservoirs and phlebotomine sandflies, the insect vectors, exist in sufficient numbers to permit frequent transmission.

During their life cycle, the parasites undergo profound morphological and biochemical changes (Fig. 1). The spindle-shaped, flagellated procyclic promastigotes proliferate in the gut of the sandfly and differentiate into the non-dividing infective metacyclic cells. When the insect feeds on a mammal, the metacyclics are transmitted into the skin and are rapidly taken up by host macrophages. The low-pH hydrolytic environment in the lysosome and the elevated temperature in the mammal induce the transformation of the promastigotes into the oval, non-motile amastigotes. Amastigotes, the second proliferative stage of the parasite, are smaller than promastigotes and have a rudimentary flagellum buried in the flagellar pocket. Amastigote proliferation ultimately leads to the rupture of the macrophages and liberated amastigotes can subsequently enter new host cells. Both, differentiation and proliferation of *Leishmania* are likely to be regulated by protein kinases and phosphatases. Therefore, these proteins represent potential targets for inhibitors which could be used as drugs to treat leishmaniasis.

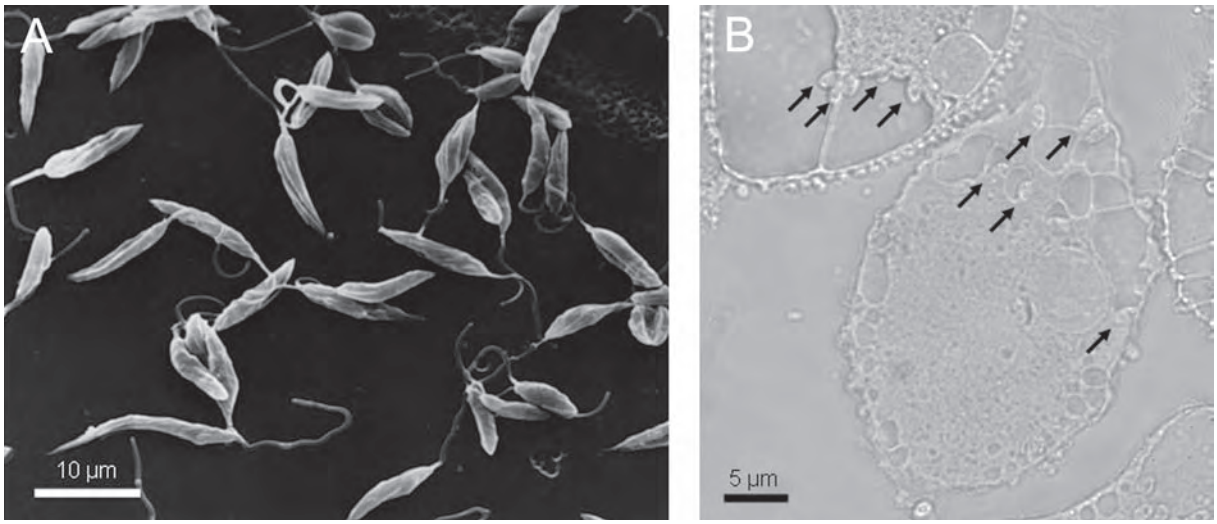

Figure 1: *Leishmania mexicana* promastigotes (A) and amastigotes in infected murine macrophages (B)

Project Description and Results

We analyse protein kinases of the mitogen-activated protein (MAP) kinase signal transduction pathways focussing on MAP kinase kinases and their substrates the MAP kinases. To gain information about the function of these proteins in the parasite we perform deletion analyses by homologous recombination and replacement of target genes by selectable resistance marker genes. Homozygous deletion mutants are analysed with regard to their morphology and their infectivity towards macrophages *in vitro* and Balb/c mice. Moreover, we characterize the recombinant protein in kinase assays, which can principally be developed further into screening assays for specific inhibitors of the respective kinase, if this enzyme turns out to be essential for the survival of the amastigote stage of the parasite, thus being a suitable drug target.

We were able to generate null mutants for the MAP kinase kinase LmxPK4 and the MAP kinase LmxMPK9 from *Leishmania mexicana*. ΔLmxMPK9 mutants showed no significant reduction in their potential to infect Balb/c mice. However, promastigotes of the null mutant revealed elongated flagella as compared to the wild type. In fact, the protein was only detectable in the "flagellated" promastigote life stage indicating a specific role in these cells. Overexpression of *LmxMPK9* led to cells with shortened flagella confirming a role of the kinase in flagellar length regulation. LmxPK4 was also restricted to the promastigote life stage. However, the null mutants displayed a defect in infectivity which in some cells could be compensated by a yet unknown mechanism and led to delayed lesion development in infected mice (Fig. 2). As the kinase is detectable during the differentiation from promastigotes to amastigotes our results suggest that LmxPK4 is required for proper differentiation and thus affects virulence of *Leishmania mexicana*.

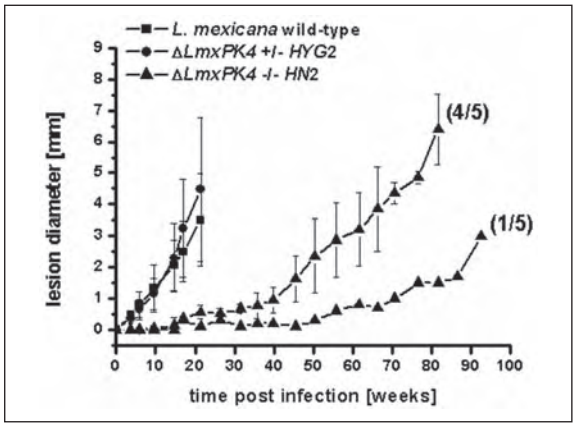

Figure 2: Infection of Balb/c mice with *Leishmania mexicana* wild type and LmxPK4 deficient mutants

As all attempts to generate homozygous deletion mutants for the MAP kinase LmxMPK4 failed, we first introduced a wild type copy of the gene on an episome and replaced the genomic copies subsequently by homologous recombination. We could prove by single-cell polymerase chain reaction (PCR) that both cultured promastigotes and amastigotes isolated from Balb/c mice retained the plasmid carrying *LmxMPK4* for a prolonged period without antibiotic selection. We conclude that LmxMPK4 is essential for both life stages of *Leishmania mexicana*. Thus, LmxMPK4 is a suitable drug target and will be forwarded to assay development including the identification of its activator and natural substrate(s).

Selected Publications

- Erdmann M, Scholz A, Melzer IM, Schmetz C, Wiese M. **2005**. Interacting protein kinases involved in the regulation of flagellar length. Mol Biol Cell: in press
- Wang Q, Melzer IM, Kruse M, Sander-Jülch C, Wiese M. **2005**. LmxMPK4, a mitogen-activated protein (MAP) kinase homologue essential for promastigotes and amastigotes of *Leishmania mexicana*. Kinetoplastid Biol Dis, Dec 29;4:6
- Kuhn D, Wiese M. **2005**. LmxPK4, a MAP kinase kinase homologue of *Leishmania mexicana* with a potential role in parasite differentiation. Mol Microbiol 56(5):1169-1182
- Bengs F, Scholz A, Kuhn D, Wiese M. **2005**. LmxMPK9, a mitogen-activated protein kinase homologue affects flagellar length in *Leishmania mexicana.* Mol Microbiol 55(5): 1606-1616

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- Andrea MacDonald
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- Angelika Schmidt
- Anne Scholz

Survival strategies of *Plasmodium* parasites in hepatocytes

Research Group Heussler (Malaria I)

Zusammenfassung

Parasiten der Gattung *Plasmodium* werden beim Stich einer infizierten *Anopheles*-Mücke auf den Säugerwirt übertragen. Mit dem Blutstrom gelangen die Parasiten schnell zur Leber, wo sie in Leberzellen eindringen und sich dort zu großen Leberschizonten entwickeln, bevor sie als Merozoiten freigesetzt werden, die dann rote Blutzellen befallen. Wir gehen der Frage nach, wie der Parasit in der Wirtszelle überlebt und wie Merozoiten schließlich von den Leberzellen zurück in den Blutstrom des Wirtes gelangen. Dabei arbeiten wir hauptsächlich mit dem Nagerparasiten *P. berghei*, um die *in vitro* gewonnenen Ergebnisse auch *in vivo* bestätigen zu können. Durch den Einsatz der Intravitalmikroskopie, bei der fluoreszierende Parasiten in einem freigelegten Leberlappen einer betäubten Maus untersucht wurden, konnten wir den Prozess der Merozoitenwanderung von den infizierten Leberzellen in die Blutgefäße nachweisen.

Summary

Parasites of the genus *Plasmodium* are transmitted to the mammalian host by the bite of an infected *Anopheles* mosquito. Sporozoites are rapidly transported with the blood stream to the liver where they infect hepatocytes and develop to large liver schizonts and, subsequently, to merozoites, which represent the infectious stage for red blood cells. In order to investigate how *Plasmodium* parasites survive in hepatocytes and how merozoites finally reach the blood stream in the liver, we use the rodent model parasite *P. berghei*. Fluorescent parasites allowed us to investigate the liberation of merozoites from infected hepatocytes into blood vessels of the liver by applying intravital microscopy of surgically exposed liver lobs of anaesthetised mice.

Project Description and Results

Our working hypothesis is that intracellular *Plasmodium* parasites support survival of the host hepatocyte during schizogony but induce host cell death during merozoite formation to assist parasite liberation from the infected cell. We investigated *P. berghei*-infected hepatocytes one and two days after infection and found an increasing level of resistance to programmed cell death (apoptosis) induced by peroxide and serum deprivation. These treatments initiated *in vitro* apoptosis in non-infected cells whereas the vast majority of parasitized cells appeared protected. Even more importantly, *in vivo* infected hepatocytes were also found protected from apoptosis induced by TNF-α confirming that *Plasmodium* exoerythrocytic forms interfere with host cell apoptosis. These data suggest that it is important for the parasite to constantly control the viability of the host cell during its intracellular development. In order to unravel the molecular mechanism of this parasite-dependent inhibition of host cell apoptosis, we started to investigate signalling pathways, which are known to support cell survival.

So far we have analysed the NF-κB, the PI3-K and the MAPK (mitogen activated protein kinase) pathway in *P. berghei*-infected hepatocytes. Whereas the NF-κB and the PI3-K pathways are not constitutively activated and inhibition of the PI3-K pathway does not affect cells harbouring developing schizonts, drug-mediated interference with the MAPK pathway inhibits parasite development in hepatocytes. It is reasonable to assume that infection and the fast growing parasite activates stress signalling in the host cell via MAPK but, on the other hand, the drug might also inhibit MAPK signalling of the parasite. So far two MAPK homologues have been identified in *Plasmodium* parasites, and we have evidence that *P. berghei* MAPK 1 is localized in the PVM of infected hepatocytes and thus has access to the host cell cytoplasm including its signalling machinery. It is therefore an attractive hypothesis that host cell MAPK kinases, which are activated by cell stress, induce parasite MAPK signalling in the PVM.

We have previously shown *in vitro* that upon merozoite formation, infected hepatocytes detach and float into the culture medium (Fig. 1A). A closer examination of detached cells revealed that parasite-filled vesicles separated from the infected cell (Fig. 1B) and it was an important goal to confirm this phenomenon also *in vivo*. Histological analysis of *P. berghei*-infected mouse livers indicated that large parasite-filled structures were bulged into liver blood vessels (Fig. 1C). In order to show the dynamics of this event, we employed intravital microscopy to analyse surgically exposed infected mouse livers during the late phase of liver infection. This *in vivo* data clearly confirmed that merozoites are released into the blood stream in vesicles, which we named merosomes (Fig. 1D).

Although detached cells exhibit many signs of cell death, host cell caspases are not involved in this process. However, there is evidence that parasite proteases of the SERA family, which are released into the host cell cytoplasm during merozoite formation, are responsible for the observed signs of host cell death. Dead cells are normally immediately removed by phagocytes, which recognise phosphatidyl serine (PS) residues on the surface of the dying cell and it was crucial to investigate why infected cells are not attacked although they exhibit signs of cell death late in infection. We could show that viable intracellular merozoites actively accumulate Ca2+. This way, the parasite inhibits exposure of PS residues on the surface of infected cells and thus avoids attack of phagocytes.

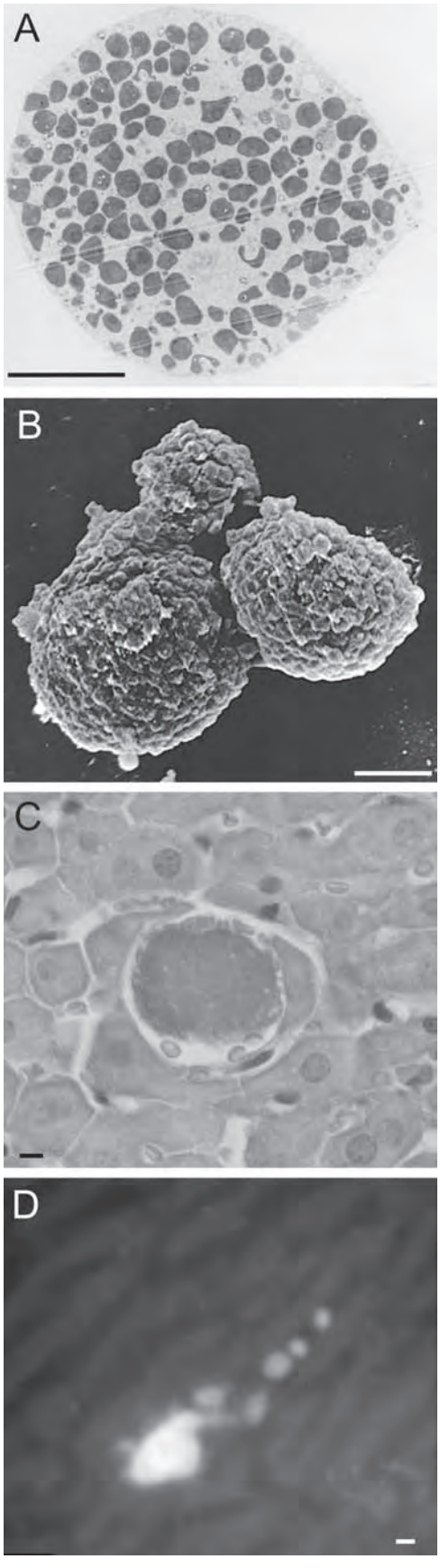

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Figure 1: Scanning and transmission electron microscopy of parasite-filled vesicles (merosomes) *in vitro* (A and B). Histological image (C) and intravital microscopy of merosome formation *in vivo* (D). Scale bar = 10 µm

The central hub for protein sorting: Re-defining the Golgi complex in *Plasmodium falciparum*

Research Group Gilberger (Malaria II)

Zusammenfassung

Der zielgerichtete und differentielle Proteintransport im Malariaparasit *Plasmodium falciparum* ist von entscheidender Bedeutung für das Überleben des Krankheitserregers in den verschiedenen Wirtszellen. Der Parasit verfügt über einen klassischen sekretorischen Transportweg, dessen integrale Bestandteile das endoplasmatische Retikulum (ER), der Golgi-Apparat (GA) und die sekretorischen Vesikel sind. Obwohl der GA eine herausragende Stellung bei der Lenkung der Proteine zu ihren subzellulären Bestimmungsorten und der post-translationalen Proteinmodifikation spielt, ist über die Morphologie, Funktion und Biogenese dieses Organells im Parasiten wenig bekannt. Mit Hilfe von GFP-fusionierten Marker Proteinen und konfokaler Mikroskopie konnte der GA im lebenden Parasiten erstmalig visualisiert, die Biogenese dieses Organells verfolgt und die räumliche Organisation untersucht werden.

Introduction

The complex biology of the intracellular parasite *Plasmodium falciparum* is a major obstacle in the design and development of new anti-malarial strategies. After an initial multiplication step in liver cells, the parasite invades and multiplies within red blood cells. In order to survive, the parasite extensively modifies the host cell by exporting proteins to the host cell cytoplasm and further to its cell surface. Secreted proteins are synthesized in the parasite cytoplasm and translocated into the ER. This is mediated through a classical hydrophobic leader sequence, although some can be considerably recessed. A membranous structure known as the Golgi is the central hub of the eukaryotic secretory machinery and plays a pivotal role in protein modification, processing and sorting. In general, the Golgi is organized into three functionally distinct regions: the *cis*-Golgi network (entry face), the Golgi stack and the *trans*-Golgi network (exit face). The ordered structure of this organelle is believed to reflect the requirement for the processing machinery to be compartmentalized for a sequential series of modification and sorting events. It is important to note that although the parasite displays a classical secretory pathway the morphological and functional evidence for a Golgi apparatus and post-Golgi transport pathways in *Plasmodium* is still rather sparse.

Project Description and Results

In order to get a better understanding of this intriguing organelle and its spatial relation with the ER, we are using GFP-tagged Golgi markers and live imaging. We identified and characterized novel Golgi proteins in the genome of the parasite. One of them termed *Pf*GRASP is a homologue of the Golgi re-assembly stacking protein (GRASP) family. GRASP proteins are peripheral membrane proteins involved in the stacking of Golgi cisternae. They define the Golgi and (with other proteins) provide an exoskeleton for this organelle.

*Pf*GRASP is transcribed and expressed throughout the asexual life cycle

Pfgrasp gene transcription was analyzed by Real Time RT-PCR throughout the asexual blood stages of the parasite. A stage specific control was performed using the early transcribed gene *etramp*. While transcription of *etramp* culminates in early stages (compared to levels of *actin* transcription), *Pfgrasp* is transcribed broadly across the asexual life cycle (Fig. 1).
This is reflected in the protein expression pattern of *Pf*GRASP. Stage specific immunoblots using *Pf*GRASP specific antibodies on synchronized parasite pellets show a major band at 70 kDa throughout the asexual life cycle (apparent M_r of *Pf*GRASP is 69 x 10^3).

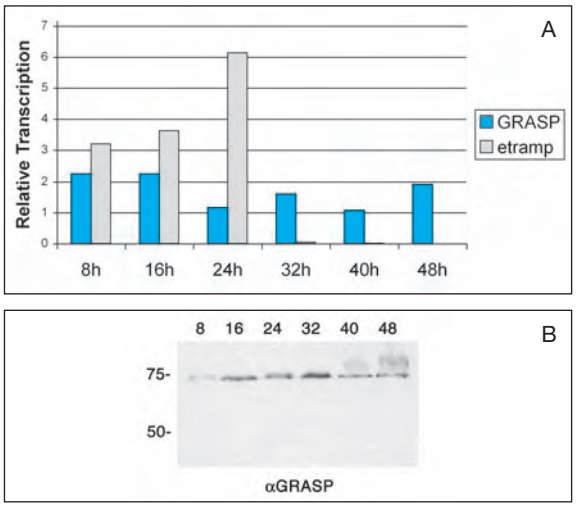

Figure 1: Expression of *Pf*GRASP in the asexual blood stages. **A.** Transcription of *Pfgrasp* (blue) was analyzed by Real Time RT-PCR using total RNA extracted from tightly synchronized parasites every 8 hours. A stage specific control was performed using the early transcribed *etramp* gene (grey). Relative gene expression is shown in bar graphs. This ratio was calculated by comparing the average transcription of *Pfgrasp* and *etramp* with transcription of the housekeeping gene *actin*, which was set to 1. Relative quantification through Real Time RT PCR showed no stage specific gene regulation for *Pfgrasp*. **B.** Immunoblot analysis of wild type parasites (3D7). Proteins from synchronized parasite cultures were separated by SDS-PAGE on a 10% gel under reducing conditions. Approximately equal amounts of parasite protein were loaded. Using anti-*Pf*GRASP specific antibodies one major 70 kDa band can be detected throughout the asexual life cycle.

_Pf_GRASP can be tagged with GFP and defines the Golgi as a perinuclear organelle

To circumvent fixation artefacts and membrane destruction we generated transgenic *Pf*GRASP-GFP expressing parasites and tracked this protein *in vivo*. Furthermore, we fused other (putative) Golgi proteins with GFP and investigated their spatial distribution during the asexual life cycle. The chimeric protein *Pf*GRASP-GFP is restricted to a tightly defined compartment juxtaposed to the nucleus in trophozoites in early parasite stages. Fig. 2)

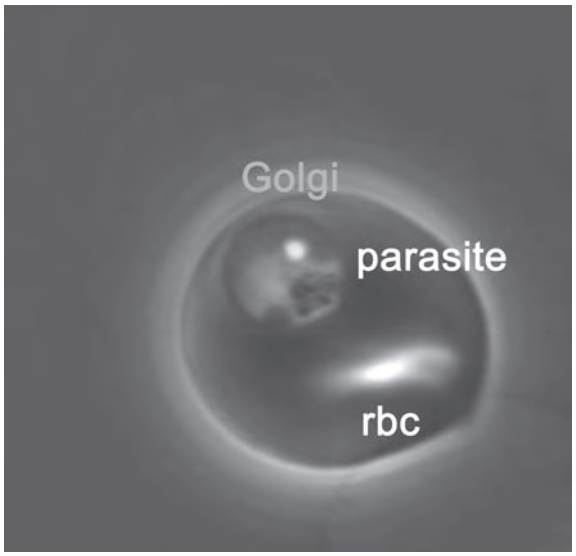

Figure 2: Localization of *Pf*GRASP by confocal and fluorescence microscopy in young transgenic parasites (<16 hours post invasion). **A.** Full length *Pf*GRASP is expressed as a GFP-fusion protein. Using fluorescence of the GFP reporter protein in live cells, *Pf*GRASP-GFP distribution (blue, forced false color) is restricted to one compartment – the Golgi – within the parasite (rbc: red blood cell).

PfGRASP co-localizes with the *cis*-Golgi marker ERD2

To further establish *Pf*GRASP-GFP as a marker for the Golgi and to generate more data with respect to Golgi architecture in *Plasmodium* we performed immunofluorescence assays using specific antibodies against previously described marker proteins for the ER and Golgi. Specifically, we used antibodies against the ER marker BiP (a luminal chaperone), the cis-Golgi marker ERD2 and the trans-Golgi marker Rab6. The *cis*-Golgi Marker *Pf*ERD2 shows co-localization to *Pf*GRASP-GFP, suggesting identity of these cellular compartments. Anti-*Pf*BiP visualizes the ER as a ring of fluorescence encircling the parasite's nucleus. Parts of this membranous system are two protrusions (ER exit sites) extending from the nuclear envelope. They lie in close proximity to but do not co-localize with the *Pf*GRASP-defined compartment.

PfGRASP is membrane attached via myristic acid

We could show that targeting of *Pf*GRASP to the Golgi membranes depends on a functional N-terminal myristoylation motif. Myristoylation is the covalent attachment of myristic acid to the alpha amino group of an N-terminal glycine via an amide bond. Substitution of the glycine at position 2 leads to a cytoplasmic variant of *Pf*GRASP-GFP.

Golgi division precedes nuclear division in the asexual life cycle

The life cycle of *Plasmodium* is completed within 48 hours and as a result up to 32 daughter parasites are released into the blood stream. Therefore, during schizogony (asexual cell division) not only duplication but coordinated multiplication of all organelles and membranous systems is essential to ensure that each merozoite inherits one complete set. We used *Pf*GRASP-GFP expressing parasites to visualize Golgi dynamics throughout the asexual life cycle. 8-16 h post invasion: One single Golgi compartment in close proximity to the nucleus can be observed. 24 h post invasion: As the parasite develops, but prior to nuclear division, a second Golgi is formed. 32-46 h post invasion: As nuclear division commences, further Golgi multiplication occurs. This results in a multiplicity of Golgi compartments ensuring that each merozoite inherits one. 0 h post invasion: A free merozoite displays one single Golgi compartment.

Selected Publications

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Medical Microbiology Section

Selected Scientific Projects
Ausgewählte wissenschaftliche Projekte

Medical Microbiology Section

Chairman's Summary

The Medical Microbiology Section combines the Departments of Immunology, Virology, and Helminthology, the Central Diagnostic Unit and the animal facilities. Selected projects are described in the following reports.

The **Department of Immunology** is mainly concerned with the immune response against parasites but also performs work in basic immunology. Investigations on the role of T cells in malaria show a dichotomy between immunopathogenetic influence and protective function. Negatively regulating ligands on T cells such as CTLA-4, PD-1 or BTLA, play a decisive role in the restriction of immunopathology. The work on *T. cruzi* led to the interesting observation that the parasite uses certain Siglecs, sialic acid-binding lectins with a still undefined regulatory function, to enter the cells (Dr. Thomas Jacobs). The still unknown function of the CD83 molecule, a member of the immunoglobulin superfamily, is analysed. Transgenic mice with ectopic expression of CD83 show that CD83 has a function both in the generation of T cells and in the peripheral immune response (Dr. Minka Breloer). Since May 2004 Dr. Uwe Ritter characterizes the function of epidermal Langerhans cells in the model of experimental Leishmaniasis. His group has gathered evidence that Langerhans cells have a regulatory function and are not the precursors of the interdigitating dendritic cells in the lymph nodes.

Prof. Herbert Schmitz, since 1979 head of the **Department of Virology** retired October 2005. PD Dr. Stephan Günther was selected as his successor. Scientific work in the Department of Virology was mainly concerned with haemorrhagic fever viruses, Lassavirus replication, the epidemiology and pathogenesis of Lassa fever and novel diagnostic procedures. The assembly of dengue and yellow fever viruses was analysed (Dr. Beate Kümmerer). The RNA helicase complex of Flaviviruses and Arenaviruses was investigated with respect to sensitivity to different lead substances with the aim of defining new inhibitor molecules by the group of PD Dr. Peter Borowski, who in 2005 left for a professorship at the Polish Academy of Sciences, Warsaw. The role of glycosylation of the V3 loop of HIV-1 gp120 protein for viral tropism and neutralization was investigated in a collaborative project with the University of Hamburg (Dr. Michael Schreiber). A **Research Group on Clinical Virology** was established in 2005 and Dr. Christian Drosten appointed as head. For the diagnosis of cases with virus-induced acute haemorrhagic fever (VHF) in Germany and other European countries, an emergency diagnostic procedure is established. On average a final result is obtained within 6 hours after arrival of the blood specimens in the L4 laboratory. A 24 h emergency hotline is installed and can be reached day and night via 0049-40-42818-0. Planning and approval procedure of the new biosafety level (BSL) 4 laboratory was facilitated by the experience of the Department in operating a BSL4 laboratory for more than 20 years. Again, experts from several other European countries came to obtain advice about construction and maintaining of such a laboratory.

Helminthology research was continued, still in the absence of a head of the Department of Helminthology. Work concerned the localisation and characterisation of antigens of *O. volvulus* (Prof. D.W. Büttner) and the generation and testing of DNA vaccines against filarial infection (PD Dr. Klaus Erttmann). A laboratory group for research on the immunology of filariasis was established in 2004 that uses *Litomosoides sigmodontis* as a model for lymphatic filariasis (Dr. Simone Korten).

The **Central Diagnostic Unit** consists of combined laboratories from the Departments of Immunology, Virology and Molecular Parasitology. It performs the direct identification of parasites, bacteria and viruses by microscopy, cultivation and molecular detection tests as well as the serodiagnosis of parasitic, bacterial and viral infections. New diagnostic methods developed by the research laboratories are evaluated and eventually incorporated into the diagnostic routine. Since 2002 the Central Diagnostic Unit is appointed by the Federal Ministry of Health as the National Reference Centre for Tropical Infections. Because of its specialization the Unit receives material submitted from all parts of Germany and also from Denmark and Austria.

Due to the demolition of the **animal house** animal experimentation had to be accommodated in the main institute building and consequently had to be reduced for the time of construction of the new extension wing. Experimental investigations in animals are an essential component of research in Tropical Medicine. Certain parasites can only be maintained by passage in animals and immunization for producing monoclonal and polyclonal antibodies has to be performed in animals. The Laboratory Animal Facility cooperates in a number these scientific projects and it supports and advises scientists in planning and executing such experimentation in accordance with the regulations of the Animal Protection Law.

Bernhard Fleischer

Zusammenfassung des Sprechers

In der Sektion Medizinische Mikrobiologie sind die Abteilungen für Immunologie und Virologie, die Mikrobiologische Zentraldiagnostik (MZD) und das Tierhaus zusammengefasst. Einige der wissenschaftlichen Projekte sind in den folgenden Projektbeschreibungen dargestellt.

Die Arbeiten der **Abteilung für Immunologie** beschäftigen sich vorwiegend mit der Immunantwort gegen parasitäre Infektionserreger, aber auch mit grundlegenden Fragen der Immunologie. Die Arbeiten betreffen die Rolle von T-Zellen bei der Pathogenese der Malaria sowie die Entwicklung neuer Methoden der Immunisierung gegen Plasmodien, beides insbesondere durchgeführt im Modell der *Plasmodium berghei* Infektion der Maus. Die Bedeutung negativ-regulierender Liganden der T-Zellen, wie CTLA-4, PD-1 und BTLA, bei der Ausprägung der Pathologie der Malaria steht im Vordergrund. Die Arbeiten an *Trypanosoma cruzi* führten zu der interessanten Beobachtung, dass der Parasit sogenannte Siglecs, Neuraminsäure-bindende zelluläre Lektine des Wirtes zur Infektion benutzt, die eine regulatorische Funktion im Immunsystem besitzen (Dr. Thomas Jacobs). Ein Molekül mit noch unbekannter Funktion, CD83, wird mit Hilfe von transgenen Mäusen untersucht. Es spielt eine Rolle bei der Reifung von T-Zellen im Thymus und bei der peripheren Immunantwort (Dr. Minka Breloer). Im Mai 2004 schloss sich Dr. Uwe Ritter der Abteilung an, um ein Projekt zur Rolle der Langerhanszellen der Haut bei der experimentellen Leishmaniasis der Maus zu bearbeiten. Für die seinen Arbeiten zugrunde liegende Hypothese, daß diese Zellen eine regulatorische Funktion besitzen, hat er experimentelle Hinweise erbracht.

Der langjährige Leiter der **Abteilung Virologie**, Prof. Herbert Schmitz, ging Ende Oktober 2005 in den Ruhestand. Eine Findungskommission bestimmte aus den eingegangenen Bewerbungen Herrn PD Dr. Stephan Günther als Nachfolger, der parallel ein externes Angebot von der Universität Groningen erhalten hatte. Die wissenschaftlichen Arbeiten der Abteilung Virologie betreffen alle Aspekte des Lassavirus, die Replikation des Virus, die Epidemiologie und Diagnostik sowie Pathogenese der Erkrankung (Prof. Schmitz, Dr. Günther). In der Laborgruppe Kümmerer wird die Reifung der Viruspartikel von Gelbfiebervirus und Denguevirus analysiert. Die RNA-Helicase als Angriffspunkt der Chemotherapeutika von verschiedene Arena- und Flaviviren wurde von PD Dr. P. Borowski untersucht, der Ende 2005 eine Professur an der polnischen Akademie der Wissenschaften in Warschau übernahm. Weiterverfolgt wurde die Frage, welchen Einfluß die Glykosylierung auf die Expression oder Maskierung von neutralisierenden Epitopen des HIV hat (Dr. Michael Schreiber). Eine **Arbeitsgruppe für Klinische Virologie**, geleitet von Dr. Christian Drosten, wurde eingerichtet, die neue molekulare Nachweisverfahren für Viren etabliert und anwendet.

Für Fälle von viralem hämorrhagischen Fieber besteht ein Bereitschaftsdienst der Virologie, da durch die aufwendigen Quarantäne- und Sicherheitsmaßnahmen eine schnelle Diagnose innerhalb von Stunden nötig ist. Im Durchschnitt vergehen nur 6 Stunden vom Eintreffen der Probe bis zur Diagnose. Ein Notruf wurde eingerichtet und ist über 040 428180 rund um die Uhr zu erreichen. Die Diagnostik wird kompliziert durch die Beschreibung neuer Virusstämme, die von den herkömmlichen Tests nicht erfasst werden. Die Planung und das Genehmigungsverfahren für das nun im Bau befindliche Hochsicherheitslabor nahm viel Zeit in Anspruch. Es wurde auf dem Boden einer mehr als 20jährigen Erfahrung im Betrieb eines Labors der höchsten Sicherheitsstufe geplant, daher kamen Experten aus anderen Ländern, um sich für den Bau solcher Laboratorien beraten zu lassen.

Die Leitung der Abteilung **Helminthologie** wurde noch nicht wieder besetzt. Helminthologische Arbeiten betreffen die Immunlokalisation von Antigenen und Enzymen bei *O. volvulus* (Prof. D.W. Büttner) und die Entwicklung von Impfstoffen gegen Filarien auf der Basis der DNA-Vakzinierung (PD Dr. Klaus Erttmann).

Eine neue Laborgruppe zur Erforschung der Immunologie der Filariose verwendet als Modell der lymphatischen Filariose die Infektion der BALB/c Maus mit dem Erreger *Litomosoides sigmodontis* (Dr. Simone Korten), um Fragen der Immunabwehr und der Impfung zu bearbeiten. Laufende Arbeiten charakterisieren die Rolle von NK-Zellen bei der Resistenz der der Maus gegen *Litomosoides sigmodontis*.

Die **Mikrobiologische Zentraldiagnostik** des BNI führt die direkte Identifizierung von Erregern bei Patienten mit bakteriellen, parasitären und viralen Infektionen durch sowie die Serodiagnose bei Infektionen mit Bakterien, Parasiten, Rickettsien und Viren. Sie ist Nationales Referenzzentrum für tropische Infektionserreger. Wegen ihrer Spezialisierung erhält die Zentraldiagnostik Materialien aus allen Teilen Deutschlands und auch aus Dänemark und Österreich zugeschickt. Das P4-Labor wird regelmäßig für diagnostische Untersuchungen bei Verdacht auf hämorrhagisches Fieber in Anspruch genommen. Es ist in das europäische Netzwerk zur Diagnostik hämorrhagischer Fieberviren eingebunden. Neue diagnostische Methoden, die in den Forschungslaboratorien entwickelt werden, werden bewertet und schließlich in die diagnostische Routine einbezogen. So wurde z.B. ein tropentauglicher PCR-Test zur Frühdiagnose des Buruli-Ulkus im Rahmen der MZD etabliert.

Durch den Abbruch des **Tierhauses** wurde die Tierhaltung stark eingeschränkt, da nur wenige Räume innerhalb des Instituts während der Bauphase zur Verfügung stehen können. Experimentelle Untersuchungen an Tieren sind ein essentieller Bestandteil der tropenmedizinischen Forschung. Bestimmte Parasiten können nur am Leben gehalten werden, wenn sie sich in Tieren vermehren. Immunisierungen zur Gewinnung von monoklonalen und polyklonalen Antikörpern müssen in Tieren durchgeführt werden. Die Mitarbeiter des Tierhauses arbeiten in mehreren dieser wissenschaftlichen Projekte mit und unterstützen und beraten die Wissenschaftler bei der Planung und Durchführung solcher Untersuchungen in Übereinstimmung mit den Vorschriften des Tierschutzgesetzes. Der Gesundheitszustand der Tiere (ausschließlich Mäuse) ist ausgezeichnet, Untersuchungen auf Tierpathogene werden regelmäßig durchgeführt und waren immer negativ (Dr. Thomas Schüler).

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Enhancement of the protective immune response against liver stage malaria by anti-CTLA-4 treatment: Implications for vaccine development

Laboratory Jacobs in the Department of Immunology

Zusammenfassung

Die Leberphase der Malaria ist ein ideales Ziel für Impfstoffe. Das Hauptproblem ist allerdings die Induktion von CD8+ T-Zellen, die für einen Schutz in dieser Phase notwendig sind. Zu diesem Zweck haben wir die Adenylatcyclase (ACT) von *Bordetella pertussis* eingesetzt, die in der Lage ist, ihre katalytische Untereinheit in das Cytosol von CD11b-exprimierenden Antigen-präsentierenden Zellen zu translozieren. Diese Methode erlaubt das Einbringen von Antigen in den MHC-I Präsentationsweg. Daher induzierte eine Immunisierung von Mäusen mit einem Fusionsmolekül aus ACT und einem Antigen aus *P. berghei* CD8+ T-Zellen. Diese Immunantwort konnte durch eine Blockade von CTLA-4 während einer nachfolgenden Immunisierung stark gesteigert werden und führte zu einem hohen Anteil von Mäusen, die einen kompletten Malariaschutz aufwiesen. Die transiente Blockade von CTLA-4 scheint eine negative Regulation der Immunantwort zu durchbrechen und ist daher eine viel versprechende Methode, um die Effizienz von Impfstoffen zu erhöhen.

Summary

The liver stage of malaria is an ideal target for vaccines. The major problem is to elicit a $CD8^+$ T cell response that is known to confer protection during this stage. For this purpose we used the adenylate cyclase toxoid (ACT) of *Bordetella pertussis* that is capable to translocate its catalytic domain into the cytosol of CD11b-expressing professional antigen-presenting cells. This allows the delivery of antigens into the MHC class I presentation pathway. Recombinant detoxified ACT containing an epitope of the *Plasmodium berghei* circumsporozoite protein (CSP) induced a specific $CD8^+$ T cell response in mice. This response could be significantly enhanced using recombinant ACT-CSP in combination with anti-CTLA-4 during boost immunization, which was accompanied by a complete protection in a number of mice after challenge with *Plasmodium berghei* sporozoites. Transient blockade of CTLA-4 may overcome a negative regulation and hence provide a strategy to enhance the efficacy of a vaccine by amplifying the number of responding T cells.

Introduction

The life cycle of malaria parasites in mammals starts with a liver stage, during which sporozoites invade hepatocytes and replicate vigorously without provoking clinical illness. After the infected hepatocytes burst merozoites are released into the blood stream and

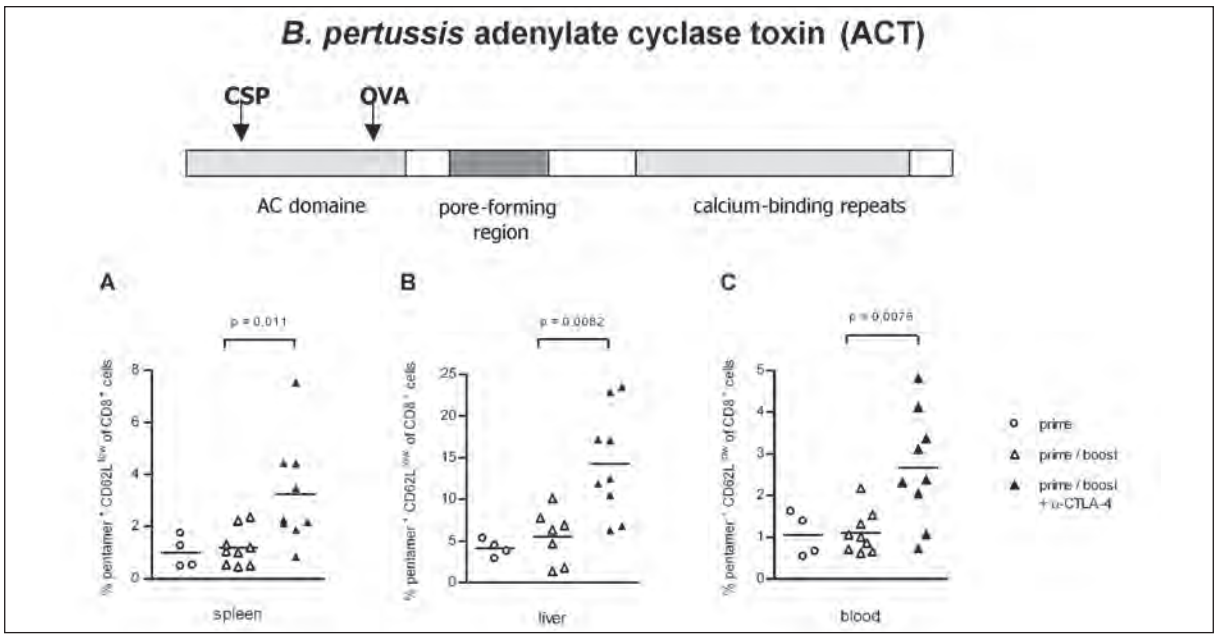

Figure 1: The detoxified *Bordetella pertussis* adenylat cyclase (upper panel) is capable to deliver its N-terminal catalytic domain into the cytosol of CD11b-expressing professional antigen-presenting cells, such as myeloid dendritic cells. This allows the use of ACT for the delivery of inserted cargo $CD8^+$ T cell epitopes into the MHC class I presentation pathway. In combination with anti-CTLA this method is capable to induce high numbers of antigen specific CD8+ T cells (lower panel).

infect red blood cells, where they undergo a massive replication. This blood stage is associated with the typical symptoms of malaria caused by the production of pro-inflammatory cytokines. Therefore, strategies to enhance the cellular immune response during the blood stage might lead to an exacerbation of disease. Taking this into account several vaccine strategies focused on the liver stage where a protection is achievable by MHC-I restricted $CD8^+$ T cells. Although several methods were employed to induce CSP-specific T cells the degree of protection often varies. Therefore, novel techniques are needed to introduce antigens into the MHC-class I presentation pathway. Furthermore, T cell activation is controlled by expression of CTLA-4 (CD152), which is a potent negative regulator of the immune system. Thus, manipulating CTLA-4 interactions became a valuable target for immunological therapies including the use of anti-CTLA-4 Abs to enhance the effectiveness of vaccines.

Project Description and Results

In the present study we used recombinant detoxified adenylate cyclase toxoid (ACT) of *Bordetella pertussis* containing an epitope of *Plasmodium berghei* CSP. ACT is capable of delivering its N-terminal catalytic domain into the cytosol of CD11b-expressing professional antigen-presenting cells, such as myeloid dendritic cells. This allows the use of ACT for the delivery of inserted cargo $CD8^+$ T cell epitopes into the MHC class I presentation pathway. Indeed, immunization of mice with ACT-CSP was sufficient to induce high numbers of CSP-specific $CD8^+$ T cells, which could be detected using a fluorescence-labelled H-$2K^d$ pentamer loaded with CSP-peptide. In addition, high numbers of cells producing IFN-γ were detected in splenocyte suspensions upon *ex-vivo* re-stimulation. A prime-boost immunization regimen did not result in any further enhancement of frequency of CSP-specific T cells secreting IFN-γ suggesting that expansion of the response following booster immunization with ACT-CSP was suppressed. CTLA-4 expression on either Treg cells or on activated T cells was previously reported to dampen the immune response, suggesting that a blockade of CTLA-4 during immunization with ACT-CSP might provide a tool for further enhancement of the frequency of induced CSP-specific T cells. To test this strategy anti-CTLA-4 treatment was included during immunization. Indeed, when anti-CTLA-4 was administered during the boost immunization with ACT-CSP an increased number of CSP-specific IFN-γ producing cells were detected. This strategy resulted in a significant degree of protection with 60 % of animals being fully protected and not developing any parasitaemia. Thus blockade of CTLA-4 is an effective method to amplify vaccine-induced T cell responses.

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Autologous Heat Shock Protein 60: A danger signal to the immune system

Laboratory Breloer in the Department of Immunology

Zusammenfassung

Die Frage, ob eukaryotisches Hitzeschock Protein 60 (Hsp60) als endogenes Gefahrensignal des Immunsystems fungiert, wurde in der Vergangenheit kontrovers diskutiert. Einerseits zeigen zahlreiche Arbeiten, dass Hsp60 die Produktion von pro-inflammatorischen Zytokinen in professionellen Antigenpräsentierenden Zellen (APZ) induzieren und die primäre Aktivierung naiver T-Zellen verstärken kann. Die scheinbar durch Hsp60 verursachte Aktivierung von APZ wurde andererseits auf Endotoxine zurückgeführt, welche die rekombinanten Proteinpräparationen kontaminierten. Mit Hilfe von LPS-depletiertem Hsp60 und Hsp60, das auf der Oberfläche von eukaryotischem Zelllinien exprimiert wurde, konnten wir die biologischen Effekte von LPS und Hsp60 Protein erstmals getrennt analysieren. In dieser Studie zeigen wir, dass LPS-freies Hsp60 die Aktivierung naiver T-Zellen steigert. Diese T-Zell Aktivierung wird jedoch im Gegensatz zu der durch LPS kontaminiertem Hsp60 verursachten Steigerung nicht durch die Zytokine IL-6, TNF-α und IL-12 oder durch TLR-4 abhängige Signaltransduktion vermittelt. Der immunstimmulatorische Effekt von autologem Hsp60 ist auch *in vivo* relevant, da Mäuse, denen Hsp60-positive Tumorzellen transplantiert wurden, wesentlich länger überlebten als Mäuse, denen der parentale Tumor transplantiert wurde. Zusammengefasst zeigen unsere Daten, dass autologes Hsp60 auch unabhängig von konservierten prokaryotischen Molekülen wie LPS eine eigene biologische Funktion hat. Daher scheint Hsp60 das Immunsystem auf verschiedene Weisen zu modulieren, einmal in Assoziation mit LPS im Falle einer bakteriellen Infektion, aber auch unabhängig von LPS im Falle von massivem Virus- oder Stress-induziertem Zelltod.

Summary

A possible function of eukaryotic heat shock protein 60 (Hsp60) as endogenous danger signal has been controversially discussed in the past. Hsp60 has been shown to induce the secretion of pro-inflammatory cytokines in professional antigen presenting cells via TLR-4 signalling and to enhance the activation of T cells in primary stimulation. However, *in vitro* activation of macrophages by Hsp60 was attributed to contaminating endotoxin in the recombinant Hsp60 protein preparations. Employing LPS-depleted Hsp60 and Hsp60 expressed on the surface of eukaryotic cell lines, we were able to dissect the Hsp60 protein mediated effects from biologic effects that are mediated by prokaryotic contaminants for the first time. We showed that LPS-free Hsp60 still induces T cell activation, but in contrast to LPS-contaminated Hsp60 this activation is not mediated by TNF-α, IL-12 or IL-6 induction and does not depend on TLR-4 signalling. The immune stimulatory effect of Hsp60 is relevant *in vivo* since mice transplanted with Hsp60-positive tumors show a prolonged survival compared to mice transplanted with wild type tumors. Taken together we provide evidence that autologous Hsp60 has a biological function that is not due to contaminating pathogen-associated molecules. Therefore, we propose two different biological mechanisms by which Hsp60 modulates immune responses, one in association with LPS in bacterial infection and another in the absence of LPS in the situation of virus induced or stress induced non-apoptotic cell death.

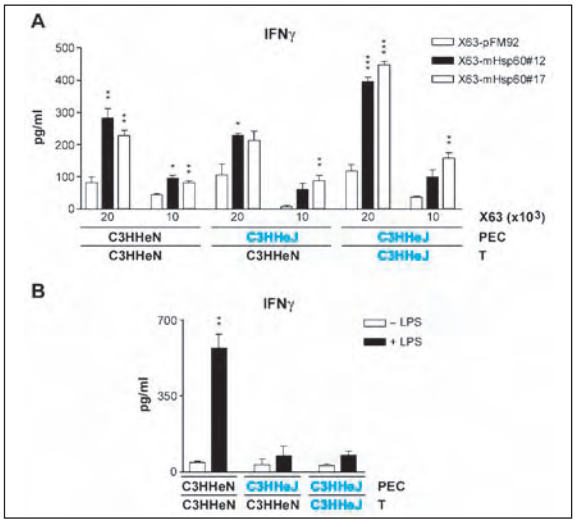

Figure 1:
Hsp60 mediated T cell activation is independent of TLR-4 $5x10^4$ T cells and $1x10^5$ macrophages prepared from TLR-4 mutant C3HheJ and syngenic C3HheN mice were cultured in indicated combinations in the presence of anti-CD3 mAb (145-2C11 0.3 µg/ml). Either $1x10^4$ cells of two different Hsp60 expressing X63 clones (black bar, grey bar 1A) or mock transfected X63 cells (white bar 1A) or LPS (1µg/ml, black bar 1B) or medium (white bar 1B) were added. IFN-γ content in the supernatant was analyzed after 24h culture. (* $p<0.05$, ** $p<0.005$, *** $p<0.0005$)

Project Results

1. LPS-free Hsp60 enhances IFN-γ production in the primary stimulation of T cells independent of IL-12 and TLR-4 signalling

We employed LPS-depleted recombinant Hsp60 and Hsp60 expressed on the cell surface of the murine cell line X63 to analyze the stimulatory capacity of Hsp60 in the absence of LPS. Addition of LPS-free Hsp60 to a T-cell stimulation culture did not induce transcription or translation of the cytokines IL-12 p70, p35, p40, TNF-α and IL-6 in the APC but still led to a significant increase of IFN-γ production in T cells (data not shown and figure 1A). By using T cells and APC derived from the TLR-4 mutant mouse strain C3H/HeJ we analyzed the role of functional TLR-4 signalling in Hsp60 mediated co-stimulation. Figure 1A shows that Hsp60 still increased the IFN-γ production in a T cell stimulation culture even if either the T cell, or the APC or both cell types carried a dysfunctional TLR-4. LPS mediated T cell activation in contrast was strictly dependent on the expression of a functional TLR-4 receptor (figure 1B).

2. More than one mechanism for the Hsp60 mediated T cell activation

Hsp60 has been shown to bind LPS and to enhance LPS mediated cytokine production in macrophages. Therefore, in bacterial infection Hsp60 released by dying cells *in vivo* may function as an LPS carrier protein that facilitates binding of LPS to the CD14/TLR-4 receptor complex and enhances LPS mediated TLR-4 signalling, similar to the LPS binding protein LBP. This situation would resemble the experiments employing recombinant Hsp60 contaminated with endotoxin *in vitro*. In the absence of LPS, for example in a viral infection or in situations of necrotic cell death Hsp60 itself may act immune stimulatory, employing a TLR-4 independent signalling pathway. This pathway does not lead to the secretion of cytokines like IL-12 by macrophages but, nevertheless, stimulates the production of IFN-γ in T cells.

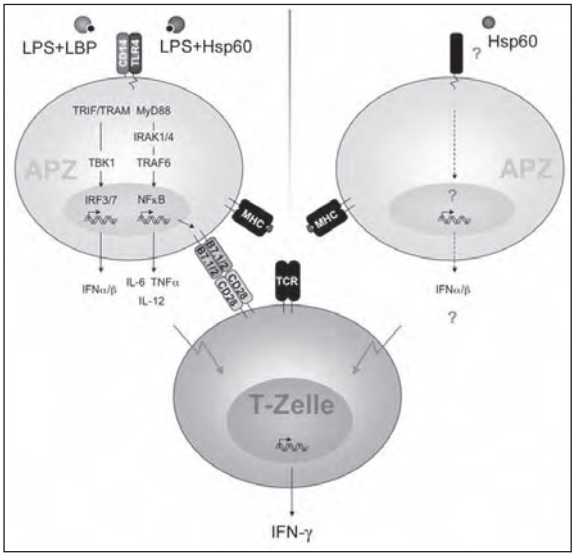

Figure 2:
Different mechanisms of Hsp60 mediated T cell activation
Hypothetical mechanism of T cell activation by Hsp60 in the presence (left panel) or in the absence (right panel) of LPS.

3. A role for Hsp60 in tumor immunology?

In order to investigate the impact of Hsp60 on tumor rejection we compared the immune response to Hsp60-negative and Hsp60-positive X63 cells. Immunization with different Hsp60 transfected X63 cells led to a significant higher frequency of IFN-γ secreting spleen cells (data not shown). Mice that were transplanted with Hsp60-positive tumor cells showed prolonged survival (Fig. 3). Taken together our data suggest that overexpression of autologous Hsp60 renders tumors more immunogenic *in vivo*.

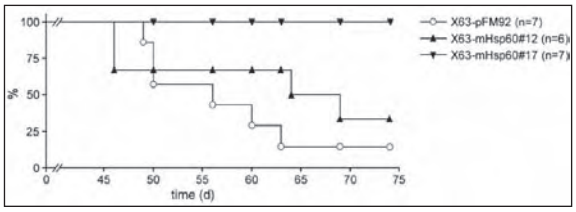

Figure 3: Hsp60-positive tumors are more immunogenic than Hsp60-negative tumors
1×10^4 Hsp60-negative (X63-pFM92) or Hsp60-positive X63 cells (X63-mHsp60#12, X63-mHsp60#17) were injected intravenously in BALB/c-mice. Survival was monitored and is indicated on the y-axis.

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- Alexandra Veit

Epidermal inoculation of *Leishmania*-antigen results in an atypical course of Leishmaniasis

Laboratory Ritter in the Department of Immunology

Zusammenfassung

Bei dem experimentellen Modell der Leishmaniose ist bekannt, dass eine Subpopulation von antigenspezifischen T-Helfer-(T_H)-Zellen den Verlauf der Krankheit bestimmt. So vermitteln IFN-γ-sezernierende T_H1-Zellen einen Schutz gegen den obligat intrazellulären Parasiten, indem infizierte Makrophagen zur Produktion leishmanizider Moleküle angeregt werden. Dendritische Zellen spielen bei der Expansion dieser T_H1-Zellen eine wichtige Rolle. So konnte gezeigt werden, dass nicht wie bisher angenommen epidermale Langerhanszellen, sondern dermale dendritische Zellen in der Lage sind, eine T-Zell-Antwort zu induzieren. Die Bedeutung von Langerhanszellen für die T_H1-vermittelte Immunantwort ist demnach neu zu bewerten. Diesbezüglich wurde eine Technik etabliert, die eine gezielte epidermale Applikation von Leishmanien-Antigen (L-Ag) ermöglicht. Nach epidermaler Applikation von L-Ag kommt es bei den ansonsten resistenten C57BL/6-Mäusen zu einem veränderten Krankheitsverlauf. Nach subkutaner Infektion zeigen die mit L-Ag exponierten Versuchstiere im Gegensatz zu Kontrolltieren folgenden Phänotyp: i) persistierende Fußpfotenschwellung, ii) verminderte antigenspezifische T-Zell-Proliferation im drainierenden Lymphknoten, iii) erhöhte Produktion von *L. major*-spezifischen IgG_1-Antikörpern. Somit führt ein epidermaler Kontakt mit L-Ag zu einer abgeschwächten T_H1-Antwort. Der zugrunde liegende Mechanismus ist Gegenstand momentaner Forschungsarbeit.

Summary

In the experimental model of Leishmaniasis it was demonstrated that a subpopulation of antigen-specific T-helper (T_h) cells is responsible for the course of Leishmaniasis. T_h1-cytokines (e.g. IFN-γ) mediate protection against the obligatory intracellular parasites by activating infected macrophages to generate leishmanicidal molecules. Dendritic cells (DCs) play a pivotal role in this T_h1-mediated immune response. Recently it was demonstrated that not Langerhans cells, as hitherto assumed, but dermal DCs are capable to induce an antigen-specific T_h1 cell response *in vivo*. Therefore, the biological impact of Langerhans cells in T_h1-mediated immune responses needs to be re-evaluated. For this aim a method was established that allows a direct application of *Leishmania*-antigen (L-Ag) into the epidermal compartment. With this approach we could demonstrate that the course of Leishmaniasis has changed in normally resistant C57BL/6 mice after epidermal L-Ag incorporation. L-Ag-exposed animals showed the following phenotype compared to control mice: i) prolonged footpad swelling, ii) diminished antigen-specific T cell proliferation in skin draining lymph nodes, iii) increased amount of *L. major*-specific IgG_1 in sera of infected mice. Taken together an epidermal contact with L-Ag results in a diminished T_h1-response. The mechanism behind this phenomenon needs to be clarified in further experiments.

Introduction

Leishmania (L.) parasites are obligatory intracellular protozoan pathogens, adapted to infect a variety of mammalian hosts. In the experimental model of Leishmaniasis mice are infected subcutaneously with promastigote *L. major* parasites. The course of disease depends on the parasite strain and the genetically determined ability of the infected mouse strain to mount an efficient immune response. A protective T_h1 response is characterized by early IFN-γ production and the expression of leishmanicidal molecules by infected macrophages. Resistant mouse strains, such as C57BL/6, are able to heal pathogen-induced skin lesions and acquire immunity. In contrast, susceptible BALB/c mice develop an IL-4 dominated T_h2-type response and succumb to a progressive generalized infection. Epidermal Langerhans cells (LCs) are discussed to be crucial for the induction of a protective immune response against *L. major*. Recently it was demonstrated that after infection with *L. major* parasites LCs migrate to the skin draining lymph node but neither harbor nor present L-Ag (Ritter *et al*. 2004, EJI 34:1542). In contrast to LCs, dermal DCs are capable to induce an antigen-specific T cell response *in vivo*. Therefore, the biological impact of Langerhans cells in T_h1-mediated immune responses needs to be re-evaluated.

Project Description and Results

To learn more about the function of epidermal LCs in T cell-mediated immune responses it is necessary to expose LCs to antigen *in vivo*. Therefore, we established a method that allows an incorporation of antigen into the epidermal compartment of the skin. We used a “gene gun” to introduce gold bullets plus antigen into the epidermal layer. In a first set of experiments we could show that targeting of epidermal LCs with ovalbumin (OVA) is sufficient to induce an antigen-specific T cell response in skin draining lymph nodes. Using this method we now have the ability to target epidermal LCs with antigen that in turn is presented to lymph node T cells. Surprisingly, the course of Leishmaniasis is noticeably altered by epidermal deposition of L-Ag. Compared to control groups L-Ag-treated mice showed

an enhanced increase of footpad thickness 30 days after infection. Furthermore, footpad swelling of L-Ag-treated mice persists up to 200 days after infection. To test whether the prolonged footpad swelling correlated with an impaired T_h1 response, proliferation assays were performed. Compared to the control groups the capability of T cells to proliferate in response to L-Ag is reduced in lymph node cells of mice that were treated with L-Ag. Furthermore, the production of L-Ag-induced IFN-γ is diminished in lymph node cells of L-Ag-treated mice. The presence of *L. major*-specific antibodies is an indication for the ability of the host organism to mount an antigen-specific immune response. Moreover, the relative contribution of the immunoglobulin isoforms IgG_{2a} and IgG_1 to the antibody response can be correlated with either a T_h1 or T_h2 response, respectively. Therefore, we analyzed the extent of the antibody reaction in L-Ag-exposed mice at the day of infection (d0) and 21 and 42 days after infection. After 21 and 42 days of infection the relative amount of *Leishmania*-specific IgG_1 is increased significantly in mice that were treated with L-Ag. In contrast, the amount of L-Ag specific IgG_{2a} is increased at day 21 after infection in mice that were bombarded with gold bullets plus L-Ag. Taken together our data indicate that epidermal contact with *Leishmania*-antigen results in an atypical course of Leishmaniasis. The molecular mechanism proposed in Figure 1 is currently under examination.

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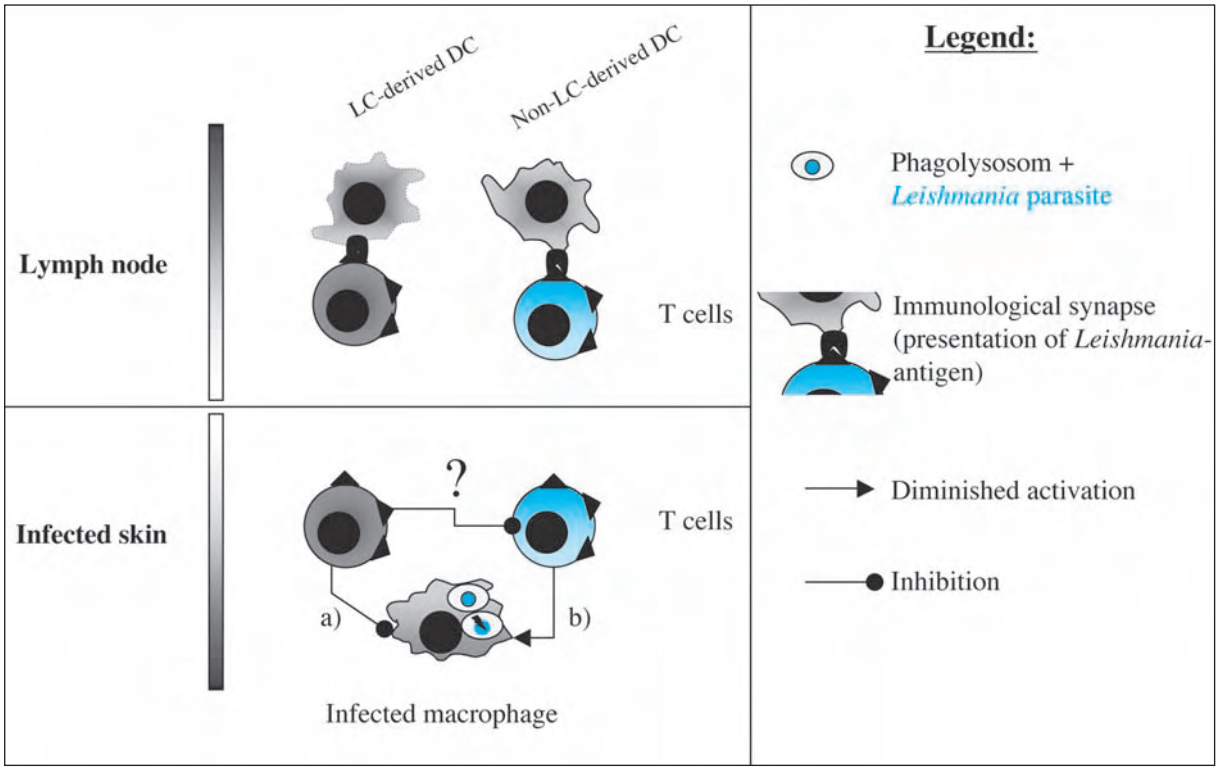

Figure 1: Targeting of epidermal Langerhans cells (LC) with *Leishmania (L.)* antigen results in a reduced capability of infected C57BL/6 mice to control intracellular *L. major* parasites. This phenomenon could be explained by two possibilities: a) The leishmanicidal activity of infected macrophages is affected by LC-primed T cells, b) LC-primed T cells suppress *Leishmania*-specific effector T cells that in turn result in a diminished leishmanicidal activity of infected macrophages. Both mechanisms will be analyzed. (Abbreviation: Dendritic cells, DC).

Establishment of a replicon system for Lassa virus

Department of Virology

Zusammenfassung

Lassa-Virus ist ein Erreger der biologischen Sicherheitsstufe 4. Die Übertragung des Virus vom natürlichen Wirt (Nagetiere der Spezies *Mastomys*) auf den Menschen kann ein tödliches hämorrhagisches Fieber zur Folge haben. Unsere Arbeitsgruppe hat mit molekulargenetischen Methoden ein Replicon-System für Lassa-Virus etabliert, mit dessen Hilfe die Mechanismen der Replikation, Transkription und Genexpression des Virus außerhalb eines Labors der Sicherheitsstufe 4 untersucht werden können. Das System ermöglicht es auch, antivirale Substanzen gegen das Virus ohne aufwändige Sicherheitsvorkehrungen zu testen.

Introduction

Lassa virus is a member of the family of *Arenaviridae*. Transmission of the virus from its reservoir (rodents of the genus *Mastomys*) to humans causes Lassa fever, an acute febrile illness associated with bleeding. The disease is endemic in the West African countries of Sierra Leone, Guinea, Liberia, and Nigeria. Bleeding, organ failure, and shock may occur in the late phase of the disease. There is no vaccination available for use in humans. The only drug with a proven therapeutic efficacy in humans with Lassa fever is the broad-spectrum nucleoside analogue ribavirin. However, the drug is only effective if given early during the course of disease. Due to the high pathogenicity of Lassa virus, and the limitations to prevent or treat infections, the virus is classified a level 4 pathogen and must be handled under biosafety level (BSL) 4 conditions.

Arenaviruses belong to the segmented negative strand RNA viruses. The genome of Lassa virus, like that of other arenaviruses, consists of two single-stranded RNA segments. The small (S) segment is 3.4 kb in length, and the large (L) segment is 7 kb in length. Replication and transcription of the genome occur in the cytoplasm of an infected cell and both take place within ribonucleoprotein (RNP) complexes. State-of-the-art for studying replication, transcription, and gene expression of negative strand RNA viruses are replicon systems. These systems are based on expression in a cell of viral genome analogs (minigenomes) as well as all viral proteins required for replication using heterologous expression systems. Within the cell, RNA and proteins assemble into RNP complexes. Replication and transcription activity of these RNPs is measured via expression of a reporter gene that had been integrated into the viral RNA analogue in place of a virus gene. Since all cis-acting elements of viral RNA and the proteins are expressed from plasmids, they can be modified by site-directed mutagenesis and functionally tested in the replicon system.

Project Description and Results

We have established a replicon system for Lassa virus. Lassa virus strain AV, which had been previously isolated from a patient with fulminant Lassa fever, was selected as a basis for the replicon system. Expression plasmids for nucleoprotein (NP), L protein (the viral RNA polymerase), and minigenome containing 5' untranslated region (UTR), intergenic region, 3' UTR, and reporter gene (Luciferase) were constructed (Fig. 1 top). Upon transfection, all components of the system were expressed in the cytoplasm by T7 RNA polymerase integrated into the host cell genome (BSR T7/5 cells) (Fig. 1 middle).

High levels of Luciferase activity were observed if minigenomes were transfected together with NP and L protein in cells (Fig. 1 bottom), showing that L protein and NP are the minimal *trans*-acting factors required for Lassa virus RNA synthesis. The minimal *cis*-acting elements are the 3' and 5' UTRs and the intergenic region. To provide more evidence for replicon functionality, the synthesis of minigenome RNA was also demonstrated by RNA blot analysis. Experiments are currently underway to explore the function of the Lassa virus polymerase (L protein) by site-directed mutagenesis.

The replicon system was also used to test antivirals outside the BSL-4 laboratory. The mode of action of ribavirin against Lassa virus is still not known. In a first attempt to narrow down the steps in the virus life cycle targeted by the drug we tested whether ribavirin inhibits the Lassa virus replicon system. Ribavirin specifically inhibited the activity of the replicon by 2 log units at concentrations of 50 µg/ml (Fig. 2A). Therefore, it is likely that the drug acts at the level of replication or transcription of Lassa virus. Recently, we have demonstrated that Lassa virus replication can also be inhibited by IFN-alpha in vitro. To test whether the Lassa virus replicon system is also susceptible to this cytokine, BSR T7/5 cells were pre-incubated with human IFN-alpha for 24 h and then transfected with the replicon components. IFN-alpha specifically inhibited replicon activity by up to 2 log units at concentrations of 1000 U/ml (Fig. 2B), suggesting that it interferes with Lassa virus replication or transcription. In conclusion, we have established the first replicon system for a highly pathogenic arenavirus. It is a tool to investigate the mechanisms of replication and transcription of Lassa virus and may facilitate the testing of antivirals outside of a biosafety level 4 laboratory.

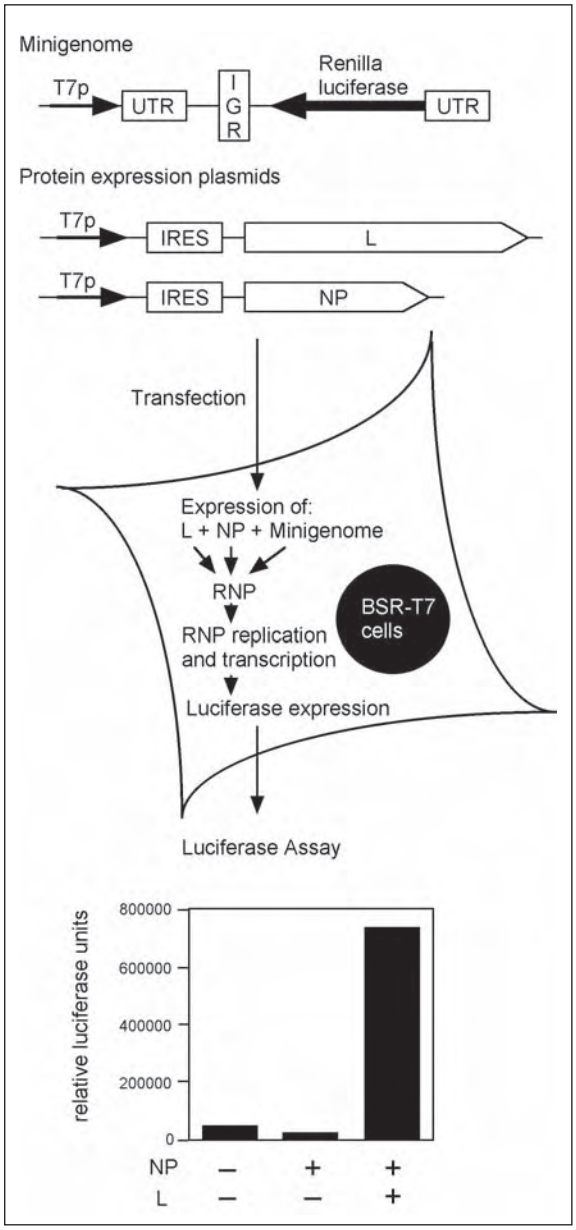

Figure 1: Flowchart of the Lassa virus replicon method. Top: Constructs for expression of minigenome, NP, and L protein (T7p, T7 RNA polymerase promoter; UTR, untranslated region; IGR, intergenic region; IRES, internal ribosomal entry site). Middle: Transfection of the constructs into BSR-T7/5 cells stably expressing T7 RNA polymerase. Bottom: Luciferase assay. Luciferase activity is only measured if both, NP and L protein are co-expressed with the minireplicon.

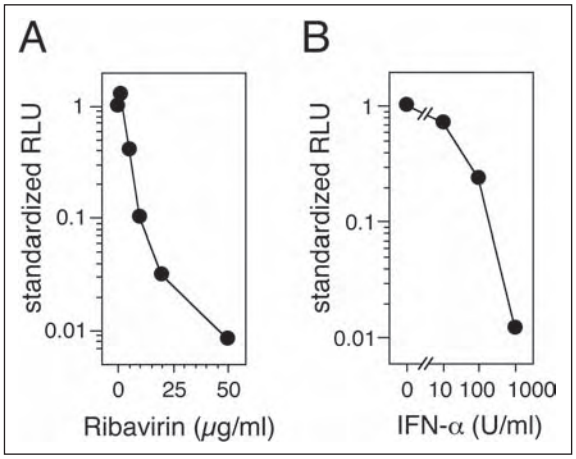

Figure 2: Inhibition of replicon activity by ribavirin and IFN-alpha. (A) Effect of ribavirin. BSR T7/5 cells were transfected with replicon components. Different concentrations of ribavirin were added 4 h after transfection. Cells were lysed 24 h post transfectionem, and luciferase activity was measured. Luciferase levels were corrected with an internal control (standardized relative light units [RLU]). The RLU in untreated cells were defined as 1. (B) Effect of IFN-alpha. Experiments were done as described above except that cells were treated with human IFN-alpha for 24 h before transfection. The same concentrations were added again 4 h after transfection. Note the logarithmic scale of the diagrams.

Selected Publications

- Hass M, Gölnitz U, Müller S, Becker-Ziaja B, and Günther S. **2004**. Replicon system for Lassa virus. J Virol 78:13793-803

Investigators

- Stephan Günther
- Beate Becker-Ziaja
- Uta Gölnitz
- Meike Hass
- Stefanie Müller

Effect of the zinc finger antiviral protein on filovirus replication

Laboratory Kuemmerer in the Department of Virology

Zusammenfassung

Kürzlich wurde beschrieben, dass das Zinkfinger antivirale Protein (ZAP) die Replikation von Retroviren und Alphaviren hemmt. Wir untersuchten weitere Viren (Ebola-, Marburg-, Lassa-, West Nil-, Dengue- und SARS Coronavirus) hinsichtlich der Hemmbarkeit durch ZAP. Dabei konnten wir zeigen, dass ZAP auch gegen Ebola- und Marburgvirus aktiv ist und dass vor allem das zweite und vierte Zinkfingermotiv des ZAP eine entscheidende Rolle bei der Hemmung der Filoviren spielt. Es wird vermutet, dass der Hemmmechanismus des ZAP über die Bindung und Destabilisierung bestimmter viraler Genomsequenzen erfolgt. Gegenstand laufender Untersuchungen ist daher die Frage, ob bestimmte Abschnitte im Genom des Ebolavirus durch ZAP destabilisiert werden.

Summary

The zinc finger antiviral protein was recently shown to inhibit retrovirus and alphavirus replication. We analyzed further viruses (Ebola, Marburg, Lassa, West Nile, Dengue and SARS coronavirus) for inhibition by ZAP. It was demonstrated that ZAP is also active against Ebola and Marburg virus and that especially the second and fourth zinc finger motif within ZAP play an important role for filovirus inhibition. The mechanism of inhibition by ZAP presumably involves binding and targeting of viral genome sequences. Therefore, we currently analyze if certain regions within the genome of Ebola virus are destabilized by ZAP.

Introduction

Ebola virus (EBOV) and Marburg virus (MARV) are single stranded negative sense RNA viruses that belong to the family Filoviridae. They cause severe hemorrhagic fever in humans and nonhuman primates. To date, no specific treatment for Marburg and Ebola hemorrhagic fever is available.

Project Description and Results

To examine the effect of ZAP expression on EBOV replication, we infected cells expressing NZAP-Zeo (Rat2-NZAP-Zeo) or control cells carrying the expression vector alone (Rat2-Zeo) with EBOV. Initially, growth of EBOV on both cell lines was assessed by indirect immunofluorescence. Rat2-NZAP-Zeo cells showed no signs of EBOV infection, whereas all Rat2-Zeo cells were infected (Fig. 1A).

To analyze the effect of NZAP-Zeo on the growth of EBOV in more detail, virus release was monitored after infection at an MOI of 0.01 and 5. Viral RNA was isolated from the supernatant and a real-time transcription-PCR assay was performed. As shown in Figure 1 B, expression of NZAP-Zeo resulted in a reduction of EBOV in the supernatant by 3 to 4 log units at both low and high MOI. In addition, we analyzed the intracellular level of EBOV specific mRNA by Northern blotting. EBOV NP mRNA was not detectable in Rat2-NZAP-Zeo cells, while there was a strong signal in Rat2-Zeo cells (Fig. 1C).

In an attempt to test the activity of NZAP-Zeo on other filovirus species, both Rat2 cell lines were infected with MARV. MARV caused a severe cytopathic effect (CPE) on Rat2-Zeo control cells. Interestingly, expression of NZAP-Zeo largely protected the Rat2 cells from a CPE (Fig. 1D), suggesting that NZAP-Zeo also has an antiviral effect on MARV.

The N-terminus of ZAP contains four CCCH-type zinc finger motifs. To determine the importance of each zinc finger for inhibition of EBOV replication, cell lines expressing NZAP-Zeo variants with single mutations in each zinc finger were infected with EBOV. Disruption of the second and fourth finger largely abolished the capability of NZAP-Zeo to inhibit growth of EBOV while disruption of the first and third finger was less important for the antiviral activity of NZAP-Zeo. These data indicate that especially the integrity of the second and fourth zinc finger motif is important for the inhibitory effect of NZAP-Zeo on EBOV replication. Both sites were also crucial for protection of cells from CPE induced by MARV.

It is assumed that ZAP acts through binding and destabilization of certain viral genome sequences. To gain insights into the mechanism by which ZAP acts against filoviruses, the sequences coding for the individual EBOV specific mRNAs have been cloned into a vector as a fusion with a luciferase reporter gene. Comparison of the luciferase levels in cells expressing NZAP-Zeo versus the control cells should shed light on the sequences targeted by ZAP.

Taken together, our data describe the first antiviral protein active against Ebola and Marburg virus. Future studies will elucidate whether ZAP plays a role in the innate response to filoviruses in humans.

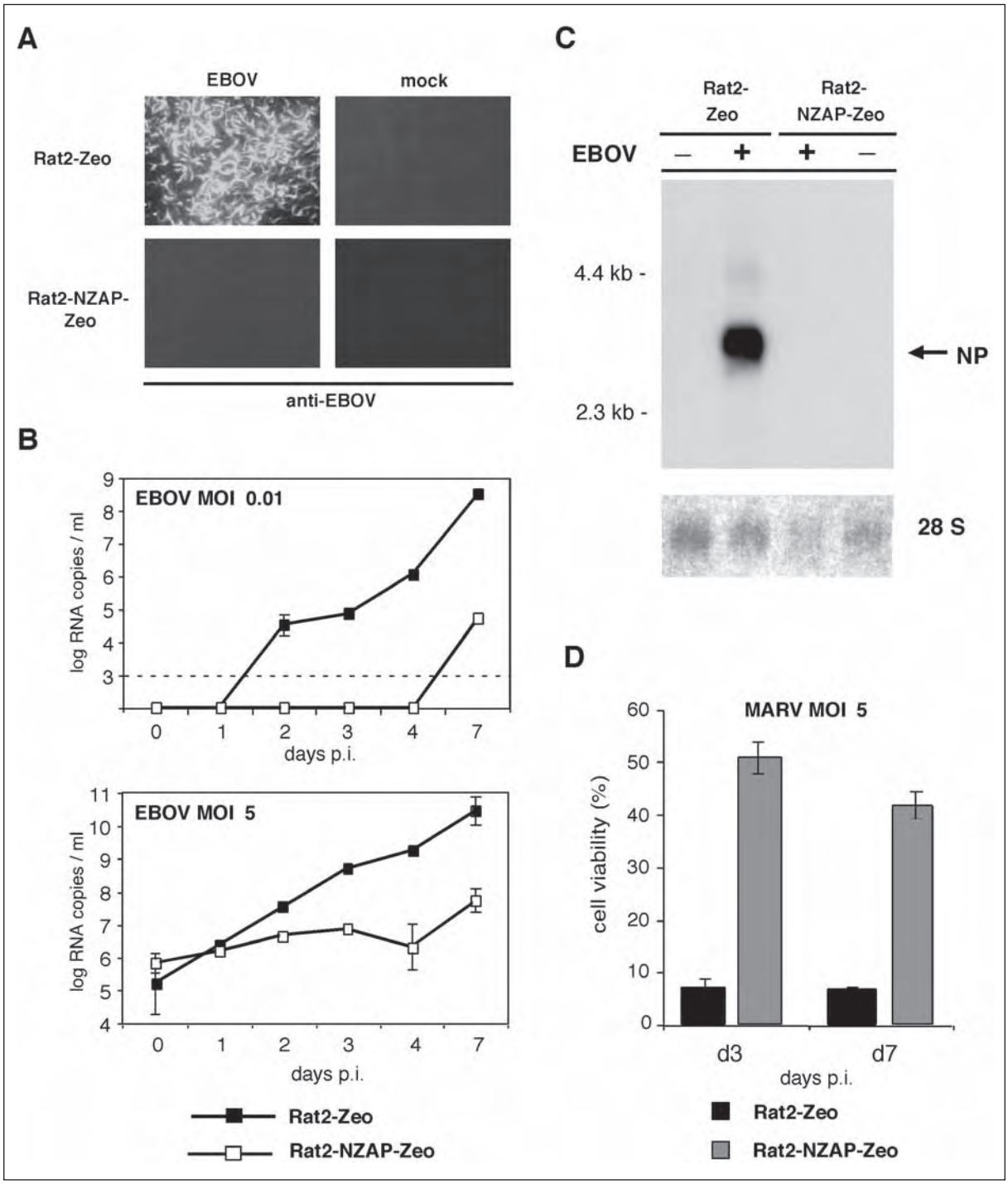

Figure 1: Effect of the zinc finger antiviral protein on Ebola virus and Marburg virus replication.
(A): Immunofluorescence analysis of NZAP-Zeo expressing cells (Rat2-NZAP-Zeo) and control cells (Rat2-Zeo) infected with EBOV using a monoclonal antibody against EBOV nucleoprotein NP.
(B): Growth kinetics of EBOV on NZAP-Zeo expressing cells analyzed by viral RNA in the supernatant using an EBOV specific real time RT-PCR.
(C): Northern blot analysis of EBOV specific RNA using a ^{32}P-labeled probe directed against EBOV nucleoprotein.
(D): Quantification of surviving cells after MARV infection measured by a cell survival assay (MTT test).

Cooperating Partners

- Stephan Becker and Peggy Möller, Philipps-University of Marburg, Germany

Investigators

- Beate Kümmerer
- Stephan Günther
- Stefanie Müller

Reverse ELISA for the selective detection of serotype-specific antibodies to West Nile and Dengue viruses

Department of Virology

Zusammenfassung

Die Domäne III des Hüllprotein-Gens des West-Nil-Virus und der Dengueviren 1 bis 4 wurde als rekombinante Antigene für einen neuen spezifischen ELISA auf Basis des Rheumafaktortests verwendet. Die verschiedenen Antigene wurden in *E.coli* exprimiert, mit denaturierender Metall-Chelatchromatographie aufgereinigt, auf der Säulenmatrix rückgefaltet und mit Meerrettich-Peroxidase direkt markiert. Der reverse Elisa ist besonders einfach durchzuführen, da Patientenserum und markiertes Antigen gleichzeitig auf die Rheumafaktor-beschichteten Mikrotiterplatten aufgebracht werden können. (Einschritt Verfahren). Der ELISA wurde bereits für drei der fünf Antigene (West-Nil-Virus, Dengue 1, Dengue 3) evaluiert. Die weitere Untersuchung mit einer größeren Zahl von West-Nil Antikörper-positiven Serumproben dauert noch an. Die bisherigen Ergebnisse weisen darauf hin, dass die starken Kreuzreaktionen von Antikörpern gegen Flaviviren (Gelbfieber, Dengue, West-Nile) nicht mehr vorkommen und dass sich unsere Antigene für die typenspezifische Diagnostik von Dengue- und West-Nil-Infektionen eignen. Mit dem Verfahren konnte bereits wahrscheinlich gemacht werden, dass West-Nil-Infektionen in Deutschland nicht vorkommen.

Introduction

It is a well-known problem that all the members of the *flavivirus* family show more or less cross reactivity in serology. Routine clinical laboratory studies do not distinguish West Nile or dengue virus infection from many other flaviviral infections. We have, therefore, developed highly specific reverse Elisas for the detection of antibodies to different flaviviruses.

Project Description and Results

In a previous study we used the *E. coli*-produced domain III (B domain) antigens of the four dengue viruses to establish an immunoblot system for determinating the serotype of dengue virus infected patients. Domain III contains type-specific epitopes. However, the problem with the system was that the immune response could not exactly be quantified. We have, therefore, established an rheumatoid factor ELISA based on our antigens.

The antigens were expressed as described already (Ludolfs et al., J Clin Microbiol 2002; 40). The purified antigen were refolded by binding them to a Nickel-NTA-column, washed with buffer containing sequentially decreased concentrations of urea, eluted with Imidazol and dialysed. The purified and refolded antigens were analyzed with SDS-PAGE to determine their protein concentration and purity.

The reverse IgG ELISA was performed as described elsewhere (Schmitz et al., J Clin Microbiol 1984;19).

An anti-domain III-antibody response was found in 24 of 25 West Nile patients (96%). The West Nile antigen differentiated reliably between sera from West Nile virus-infected patients, sera from dengue virus-infected patients and sera from normal controls. Interestingly, the antigen could not discriminate between antibodies to virus West Nile virus and the closely related Murray Valley encephalitis virus, as shown in the figure below.

For the dengue 1 antigen, 5 of 6 dengue 1-positive sera were positive in the rheumatoid factor ELISA. 6 of 6 dengue 3 positive sera, 18 West Nile positive sera and 30 negative control sera did not react with the dengue 1 antigen.

From 6 Dengue 3 positive sera, 4 were also positive with the dengue 3 antigen. None of the 16 dengue 1 positive sera tested was positive with the dengue 3 antigen and only one out of the 25 West Nile positive sera and one of the 30 negative control sera reacted with the dengue 3 antigen.

Funding

- BMG (Federal Ministry of Health)

Investigators

- Diana Ludolfs
- Herbert Schmitz

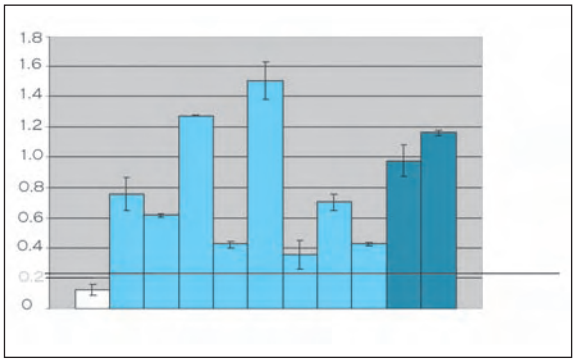

Figure 1:
Rheumatoid factor ELISA with recombinant West Nile antigen West Nile positive sera (blue), Murray Valley encephalitis positive sera (grey) and arithmetic mean of 11 negative control sera (white). The black line indicates the cut off value (0.234).

Reverse Elisa diagnostic test for antibodies to Lassavirus

Department of Virology

Zusammenfassung

Zwei hoch sensitive und spezifische reverse Immun-Enzymteste (Elisa) wurden entwickelt, um Lassavirus IgG- und IgM-Antikörper nachzuweisen. Mit einem reversen System werden zuerst die zu untersuchenden Antiköper an die Festphase gebunden. Dann erst wird die Menge des spezifischen Antikörpers durch Zugabe eines direkt oder indirekt markierten Antigens bestimmt. Für unsere reversen Teste wurden die IgG- und IgM-Antikörper der menschlichen Seren an Mikrotiter-Platten gebunden, die entweder mit Rheumafaktor oder mit anti-human µ-Ketten-Antikörpern beschichtet waren. Für beide Teste wurde ein Zell-extrahiertes Lassavirus-Antigen benutzt. Dann wurde das gebundene Antigen mit einem markierten monoklonalen anti-Lassa Nukleoprotein Antikörper nachgewiesen. In den Seren von überlebenden Lassa-Patienten konnten IgG-Antikörper mit 100% Sensitivität nachgewiesen werden. In 5 Seren, die zwei bis 8 Wochen nach Krankheitsbeginn entnommen waren, fanden sich IgM-Antikörper. In Kontrollproben von über tausend gesunden Afrikanern, die mit der indirekten Immunfluoreszenz keine spezifischen IgG- oder IgM-Antikörper aufwiesen, konnten keine IgM-Antikörper mit dem Elisa nachgewiesen werden. In der Mehrzahl diskrepanter Seren konnten zusätzlich auch mit der IIF-Antikörper nachgewiesen werden, wenn mit drei verschiedenen Lassavirus-Antigenen getestet wurde. Dann ergab sich eine Spezifität für den Elisa im Vergleich zur indirekten Immunfluoreszenz von 99,7%. Da alle Reagenzien lyophilisiert werden können, sind die reversen Elisa-Teste besonders feldtauglich.

Introduction

For the detection of acute Lassa virus infections RT-PCR has turned out to be highly sensitive and specific. However, RT-PCR is difficult to perform in field hospitals in West Africa. As an alternative to RNA detection in blood or urine specimens, simple antibody assays are urgently needed. IgG antibodies may also be helpful for diagnosing past infections and immunity and may provide insights into the epidemiology of Lassa fever infection in endemic areas.

In contrast to frequently used indirect Elisa techniques, where the antigen is bound to the solid phase and the antibody is determined indirectly by a labeled anti-immunoglobulin conjugate, we have made use of a reverse Elisa technique, where the antibody is bound to the solid phase and the amount of antigen bound is subsequently detected by labeled antigen.

Project Description and Results

In our reverse system for the IgM antibody assay anti-µ coated microtiter plates were used, while human IgG antibodies were bound to Rheumatoid factor (RF) coated plates. The RF preferentially binds immune complexes, consisting of specific IgG and antigen. Therefore, in our IgG Elisa the human serum and the antigen can be applied to the Rheumatoid factor (RF)-coated plate simultaneously.

Using the reverse Elisa technique for anti-Lassa IgG or IgM antibodies, low serum dilutions or even undiluted serum could be tested without background staining. Accordingly, both tests turned out to be highly sensitive in detecting IgG and IgM anti-Lassa antibodies. Moreover, the reverse tests were also specific, because a purified labeled monoclonal antibody was used for the detection of the Lassa antigen

1045 serum samples of healthy subjects had been collected in different countries in West Africa. The comparison of the results obtained by IgG Elisa and IIF are shown in the Table. 90 of the1045 serum samples with IgG antibodies by IIF were also positive by IgG Elisa. Six discrepant samples, negative by IIF, had low antibody titers between 1:40 and 1:160 by IgG Elisa. (Compared to the results by IIF a sensitivity of 100% and specificity 99.3% was obtained. Since antibody titers in IIF were ten-times lower compared to titers obtained by reverse IgG Elisa, such low titers might not be detectable by IIF. When testing the six false positive sera for antibodies to Lymphocytic coriomeningtis virus and Mopeia virus by IIF no antibody reactivity was found.

Investigators

- Herbert Schmitz
- Petra Emmerich

Table 1: Comparison of IIF with IgG Elisa using 1045 serum samples of healthy donors of West Africa.

		IgG Elisa positive	IgG Elisa negative	
IIF	positive	90	0	Sensitivity 100 %
	negative	4	955	Specificity 99,7%

Rabies transmitted by transplantation of solid organs in Germany

Research Group Clinical Virology

Zusammenfassung

Zum Jahreswechsel 2004/2005 verstarb eine junge Organspenderin unter unklarer neurologischer Symptomatik in der Universitätsklinik Mainz. Nach Ausschluss gängiger infektiöser Ursachen wurden Herz/Lunge, Leber, Milz, beide Nieren und die Hornhäute beider Augen an sechs Empfänger in Deutschland transplantiert. Mitte Februar traten etwa zeitgleich Symptome bei drei von sechs Empfängern auf. Nach Einleitung einer Untersuchung durch die Deutsche Stiftung Organtransplantation wurde durch das BNI die Erstdiagnose Tollwut bei den Empfängern per PCR gestellt und über Sequenzanalyse die epidemiologische Verbindung bestätigt. Aus archiviertem Hirnmaterial der Spenderin wurde der Tollwut-Nachweis zunächst über Histologie und Elektronenmikroskopie geführt, sowie durch eine direkte Immunfluoreszenzuntersuchung am Institut für Hygiene und Umwelt (Dr. S. Baumgarte). Auf der Basis der Virussequenz der Empfänger gelang die Amplifikation der Tollwut-RNA auch aus dem formalinfixierten Hirn der Spenderin, deren 100%ige Sequenzidentität den endgültigen Übertragungsnachweis erbrachte.
Ein Vergleich mit der Gen-Datenbank der amerikanischen Centers for Disease Control zeigte eine hochgradige Verwandtschaft des Virus zu indischen Tollwut-Isolaten. Die Infektionsquelle konnte damit eindeutig eingegrenzt werden: Die Organspenderin war zwei Monate vor ihrem Tod als Touristin in Indien gewesen.
Drei von sechs Organempfängern starben letztendlich an Tollwut, davon zwei innerhalb von wenigen Tagen nach der Diagnose. Ein Patient wurde acht Wochen unter maximaler Intensivtherapie behandelt, wobei eine eigens für das Patientenvirus entwickelte real-time PCR zur Beobachtung der Viruslast im Liquor cerebrospinalis verwendet wurde. Trotz intensiver Bemühungen verstarb auch dieser Patient. Der Empfänger der Leber war durch eine Impfung in seiner Kindheit geschützt und entwickelte nie Zeichen einer Infektion. Auch beide Hornhautempfänger blieben gesund.

Project Description and Results

During February 2005 in Germany, three of six recipients of organs from a single solid organ donor developed acute encephalitis and died. The donor was a young woman who had died about six weeks earlier of neurological disease of unknown origin. The simultaneous occurrence of symptoms in several donors triggered a look-back procedure, within which rabies virus was identified as the cause of symptoms in two recipients by PCR. As only archived formalin-fixed brain material was available of the organ donor, PCR could not be employed initially. However, classical methods of rabies virus detection yielded clear evidence of infection (Fig. 1). Sequencing of rabies virus RNA revealed a clear epidemiological link, as both recipients' virus sequences were 100% identical. Knowing the sequence, a strain-specific nested RT-PCR could be designed for direct sequencing in donor's brain tissue in spite of formalin fixation. Virus sequences in donor and recipients were 100% identical, proving transmission.
The virus sequence was determined as a whole directly from saliva of one of the organ recipients. A phylogenetic analysis conducted on the rabies RNA database of the Centers for Disease Control revealed close relationship of the patients´ virus with an isolate obtained ten years ago from an American patient who died after having been infected in India. Indeed, re-interview of the donor´s relatives relealed that she had been traveling to India about two months before she died, and fellow travelers reported contact with a stray dog in Goa.
Of the six organ recipients, three developed symptoms in total (Fig. 2). Two recipients of heart/lung and kidney, respectively, died within days after diagnosis. The recipient of the spleen and one kidney was treated during 8 weeks of intensive care, using neuroprotective therapy (hypothermia, neuroleptics, amantadine), post exposure active vaccination, anti-rabies hyperimmune-globulin, and empiric antiviral therapy consisting of ribavirin, alpha interferon, and amantadine (Willoughby, NEJM 2005, 352(24)). Based on the virus sequence, a strain-specific real-time RT-PCR assay was established, calibrated with a cloned and in-vitro transcribed copy of the patient's virus target sequence. Virus RNA concentration was one of the few indicators of prognosis in the deeply comatose patient. As shown in Fig. 2, the virus concentration was undetectable in cerebrospinal fluid (CSF) on the day of initial diagnosis, but reached between 1,000 and 10,000 copies/mL of CSF by day 10. It stayed so for about three weeks, before a sharp rise on day 31 gave indication of clinical deterioration. An arrest of cerebral perfusion was detected 52 days after the initial diagnosis, marking cerebral death. The liver recipient did not show any symptoms but dis-

played a steep incline in neutralizing antibodies already at the time of initial diagnosis. Re-interviewing of his parents revealed rabies vaccination in childhood. Both recipients of corneae are healthy without having been vaccinated before transplantation.
In view of similar events reported during recent years in America (Roos, Am J Neurol 2005, 62(6), Srinivasan, NEJM 2005, 352(11)), it should be considered whether elective recipients of organs should be vaccinated against rabies at the time of being enrolled in transplantation lists.

Cooperating Partners

- Sigrid Baumgarte, Institut für Hygiene und Umwelt, Hamburg
- Joachim Hoyer, Universität Marburg
- Michael Roggendorf, Universität Essen
- Charles Rupprecht, CDC Atlanta, USA

Investigators

- Marcus Panning
- Susanne Pfefferle
- Klara Tenner-Racz
- Christel Schmetz
- Christian Drosten

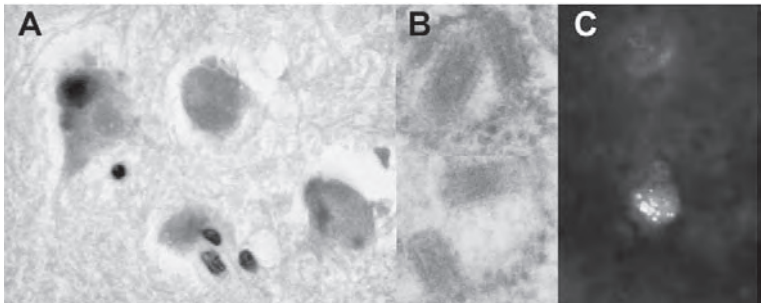

Figure 1: A, Negri bodies;
B, rabies virions budding from intracellular membranes in electron microscopy;
C, direct fluorescent staining of rabies virus antigen with an FITC-labelled antibody

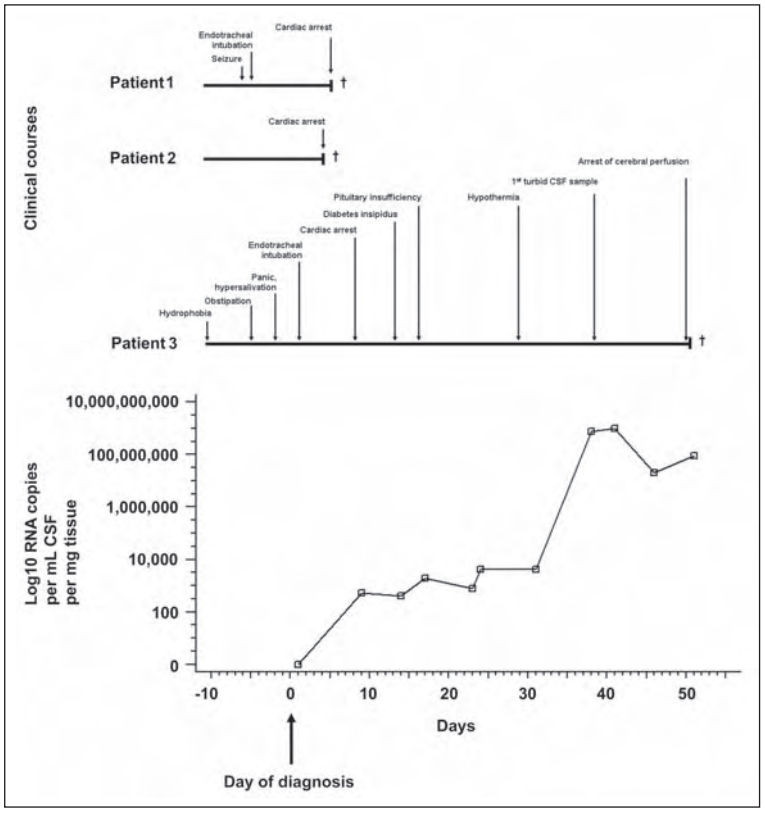

Figure 2: Clinical events during the course of recipients 1 (kidney), 2 (heart and lung), and 3 (spleen and kidney), who died of rabies. Bottom: Virus RNA concentration over time, as determined by real-time RT-PCR in cerebrospinal fluid of recipient 3.

Tropical Medicine Section

Selected Scientific Projects
Ausgewählte wissenschaftliche Projekte

Tropical Medicine Section

Chairman's Summary

The Tropical Medicine Section at present comprises the Departments of Molecular Medicine and Pathology, the Infection Epidemiology Group as well as the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), a joint research centre of the Bernhard Nocht Institute and the University of Kumasi, Ghana. With the move of the Bioinformatics Group to the Max-Planck Society in late 2002, competence in bioinformatics was sought through collaborations with the Centre for Bioinformatics of Hamburg University and the Institute of Medical Biometry and Statistics of the University of Schleswig-Holstein in Lübeck. In 2004, an Infection Epidemiology Group under the leadership of PD Dr. Jürgen May was established to meet the institute's long-standing need for expertise relevant to field and clinical studies.

Activities of the **Molecular Medicine Department** were dominated by the final stage of 4 years of recruiting in Africa >16,000 participants of genetic studies on malaria and pulmonary tuberculosis, including data management of >1.5 Mio entries (funded by the National Genome Research Network of BMBF). Patient characterizations were found to improve malaria disease definitions and to reveal new aspects of drug resistance of *Plasmodium falciparum* and *Mycobacterium tuberculosis*. Initial genetic data indicated that the large patient samples allow to form subgroups of sufficient size to dissect the complex clinical syndromes of severe malaria into pathogenically diverse entities and to identify correlations between host and pathogen variants in tuberculosis. A new test for alpha-thalassaemia was established. A family study on mild malaria revealed a region on chromosome 10 showing strong and robust linkage with the occurrence and frequency of mild disease episodes.

The **associated laboratory groups** study parasite-host interactions and immune recognition of malaria and nematode parasites, in part to complement human genetics data. Mo Klinkert`s group focuses on members of large multigene families of *P. falciparum (var, rif, stevor)*, seeking to understand cellular functions and a role in disease. Projects include (i) RIFIN expression during the life cycle, (ii) protein translocation using transfectant parasites, (iii) characterization of erythrocyte surface molecules expressed by parasites of distinct binding phenotypes and (iv) immunological analyses of recombinant variable antigens (funded by the European Commission). Diverging from mainstream research, work has also spanned developing novel chemotherapeutic strategies based on known anti-cancer drugs. To elucidate mechanisms of malaria-associated anaemia, Norbert Brattig`s group characterizes antigens of *P. falciparum* bound to the surface of uninfected erythrocytes and recognized by serum antibodies of semi-immune persons. Another project addresses putative secretory proteases of adult worms and larvae of *Onchocerca volvulus* and *Brugia malayi*, which are considered essential for mobility in human tissues as a prerequisite for parasite fertility, transmission and also pathogenicity (funded by DFG).

In national and international collaborations, the **Department of Pathology** continued studies on the pathogenesis of HIV infection in humans and on immunoprotection in the monkey HIV/AIDS model (funded by the European Commission, Gates Foundation and BMBF). Primary HIV-1 infection was accompanied by persistent depletion of mucosal CD4+ T lymphocytes in the gut which could not be corrected by HAART treatment, in contrast to near-complete recovery of blood CD4+ cells. In chronic infection all major HIV structural proteins and glycoproteins were found to persist on the surface of follicular dendritic cells of lymph node germinal centres as well as humoral responses to these antigens in the absence of detectable virus load in the plasma. Nasal immunization of monkeys with attenuated SIV or virus-like particles showed extensive hyperplasia of isolated lymphoid follicles in the nasal mucous membrane resembling intestinal Peyer`s patches and facilitating the uptake of foreign material. The role of macrophages and dendritic cells was studied in granuloma formation in human cutaneous leishmaniasis.

The **Infection Epidemiology Group** co-ordinates a multi-centre clinical trial on Intermittent Preventive Treatment in infants (IPTi), a new malaria control measure for African children. The trial is funded by BMBF, DAAD and DFG. Using KCCR facilities (see below), 1070 children were followed by more than 20,000 active and passive visits. The study includes projects on the development of parasite drug resistance and on the influence of human genetic variants on the dynamics of malarial infections in early childhood (supported by Volkswagen Foundation).

The **Kumasi Centre for Collaborative Research in Tropical Medicine** (KCCR) continued to use its well established infrastructure to support extended projects on malaria, filariasis, tuberculosis and Buruli ulcer as well as smaller studies on aflatoxin ingestion and HIV infection. The projects are summarized separately in this issue (see below). KCCR maintained its high level of research activities due to external project funds from the European Commission, the German Initiative on Malaria, the German Human Genome Research Network, and the Volkswagen Foundation.

Rolf Horstmann

Zusammenfassung des Sprechers

Die Sektion Tropenmedizin umfasst die Abteilungen für Tropenmedizinische Grundlagenforschung und Pathologie, die Arbeitsgruppe Infektionsepidemiologie sowie das *Kumasi Centre for Collaborative Research in Tropical Medicine* (KCCR), eine gemeinsame Forschungseinrichtung des Instituts und der Universität von Kumasi, Ghana. Seit die Bioinformatik-Gruppe Ende 2002 an die Max-Planck-Gesellschaft wechselte, werden Spezialkenntnisse in Bioinformatik durch enge Zusammenarbeit mit dem Interdisziplinären Zentrum für Bioinformatik der Universität Hamburg und dem Institut für Medizinische Biometrie und Statistik der Universität Schleswig-Holstein in Lübeck eingeholt. 2004 wurde unter der Leitung von PD Dr. Jürgen May eine Arbeitsgruppe für Infektionsepidemiologie gebildet, um im Institut einen langjährigen Bedarf an epidemiologischer Expertise für Feldstudien und klinische Studien zu decken.

Die Arbeit der **Abteilung für Tropenmedizinische Grundlagenforschung** war geprägt von der letzten Phase der Rekrutierung von über 16.000 Teilnehmern genetischer Studien zu Malaria und Lungentuberkulose, die eine Verarbeitung von >1,5 Mio Daten erforderte (gefördert durch das Nationale Genomforschungsnetz des BMBF). Es zeigte sich, dass die Charakterisierung großer Patientenzahlen neue Aspekte der Falldefinition von schwerer Malaria und der Medikamentenresistenz von *Plasmodium falciparum* und *Mycobacterium tuberculosis* eröffnete. Erste genetische Daten zeigen, dass die Fallzahlen ausreichend groß sind, um das komplexe Syndrom der schweren Malaria in pathogenetisch unterschiedliche Formen einzuteilen und bei Tuberkulose Zusammenhänge zwischen Wirts- und Erregervarianten zu finden. Für alpha-Thalassämien wurde eine neue Nachweismethode entwickelt. Eine Familienstudie zu milder Malaria ergab ein starkes und reproduzierbares Kopplungssignal auf Chromosom 10 mit Auftreten und Häufigkeit von milden Krankheitsepisoden.

Die der Abteilung **assoziierten Laborgruppen** untersuchen Proteine von *Plasmodium falciparum* und Nematoden, die offenbar in der Wirt-Parasit-Interaktion von besonderer Bedeutung sind. Die Gruppe von Mo Klinkert konzentriert sich auf Mitglieder der großen Gen-Familien variabler Proteine von *P. falciparum (var, rif, stevor)*, um deren Rolle in Zellbiologie und Pathogenität zu untersuchen. Aktuelle Studien betreffen (i) die Untersuchung der Expression verschiedener RIFINs während der Parasitenentwicklung, (ii) die Proteintranslokation unter Verwendung transfizierter Parasiten, (iii) die Charakterisierung spezifischer Proteine auf der Oberfläche infizierter Erythrozyten , die bestimmte Adhärenzeigenschaften aufweisen und (iv) die Antikörperreaktion infizierter Personen auf rekombinant exprimierte Varianten (gefördert durch die EU). In Ergänzung zur gängigen Medikamentensuche werden etablierte Krebsmittel *in vitro* auch auf ihre Wirkung gegen Malariaparasiten untersucht. Um die Entstehung der Malaria-Anämie zu untersuchen, charakterisiert die Gruppe von Norbert Brattig Antigene von *P. falciparum*, die sich an nicht-infizierte Erythrozyten anlagern und von Antikörpern teilimmuner Personen erkannt werden. In einem weiteren Projekt werden sezernierte Proteasen von Adulten und Larven von *Onchocerca volvulus* und *Brugia malayi* untersucht, die als essentiell für deren Beweglichkeit in menschlichem Gewebe gelten, ein wesentlicher Faktor sowohl für Vermehrung und Übertragung, als auch für die Pathogenität der Parasiten (gefördert durch die DFG).

Die **Abteilung für Pathologie** setzte in nationalen und internationalen Kooperationen ihre Studien zur Pathogenese der HIV-Infektion beim Menschen und zum Immunschutz im Affenmodell für HIV/AIDS fort (gefördert durch EU, Gates-Stiftung und BMBF). Primäre HIV-Infektionen zeigten eine anhaltende Depletion von CD4+ T-Lymphozyten in der Darmschleimhaut, die im Gegensatz zu einer fast vollständigen Erholung der CD4+-Zellen im Blut nicht durch HAART-Behandlung korrigiert werden konnte. Bei chronischen Infektionen waren alle wesentlichen Strukturproteine und Glykoproteine auf der Oberfläche von follikulären dendritischen Zellen in Keimzentren von Lymphknoten anhaltend nachweisbar, ebenso wie die Antikörperantwort gegen diese Antigene ohne nachweisbare Viruslast im Plasma. Nasale Immunisierung von Affen mit attenuiertem SIV oder virusähnlichen Partikeln verursachte eine ausgedehnte Hyperplasie isolierter Lymphfollikel der Nasenschleimhaut, die intestinalen Peyer`schen Plaques ähneln und offenbar die Aufnahme von körperfremdem Material begünstigen. Bei der humanen Hautleishmaniose wurde die Rolle von Makrophagen und dendritischen Zellen bei der Granulombildung untersucht.

Die **Arbeitsgruppe Infektionsepidemiologie** koordiniert eine klinische Multicenter-Studie zu *Intermittent Preventive Treatment in Infants* (IPTi), einer neuen Maßnahme zur Malariakontrolle bei afrikanischen Kindern. Im KCCR (siehe unten) wurden 1070 Kinder durch insgesamt mehr als 20.000 aktive oder passive Erhebungen im Verlauf untersucht. Die Studie wird von BMBF, DAAD und DFG gefördert. Sie umfasst Projekte zur Entwicklung von Medikamentenresistenz der Parasiten und zum Einfluss humaner genetischer Varianten auf die Dynamik der Malariainfektion in der frühen Kindheit (gefördert durch die VolkswagenStiftung).

Das **Kumasi Centre for Collaborative Research in Tropical Medicine** (KCCR) unterstützte mit seiner gut entwickelten Infrastruktur weiterhin umfangreiche Projekte zu Malaria, Filariosen, Tuberkulose und Buruli-Ulkus sowie kleinere Studien über Aflatoxin-Aufnahme und HIV-Infektion. Die Projekte sind in diesem Band gesondert zusammengefasst (siehe unten). Durch erhebliche Unterstützung der Europäischen Union, der deutschen Malariainitiative, des deutschen Nationalen Genomforschungsnetzes und der Volkswagenstiftung konnte das KCCR den hohen Grad seiner Aktivitäten aufrecht erhalten.

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see page 92

Complicated and uncomplicated severe malarial anaemia

Department of Molecular Medicine

Zusammenfassung

Malaria kann milde oder lebensbedrohliche Anämien verursachen. Es ist unbekannt, in welchem Ausmaß die Zerstörung parasitierter oder nichtparasitierter Erythrozyten und ineffektive Erythropoese zur Anämie beitragen, insbesondere auch bei den verschiedenen Schweregraden. Unsere klinischen Beobachtungen weisen darauf hin, dass sich auf Grund der Schnelligkeit, mit der sich die Anämie entwickelt, klinische Formen der Anämie unterscheiden lassen, die unterschiedliche supportive Behandlung erfordern.

Summary

Malarial anaemia may be mild or of life-threatening severity. It affects millions of children worldwide but little is known about how destruction of parasitized red blood cells (RBCs), destruction of non-parasitized RBCs and ineffective erythropoiesis contribute to its pathogenesis in the various degrees of severity. Our clinical studies suggest that the rapidity of its development may separate distinct clinical entities of severe anaemia, which require different supportive treatments.

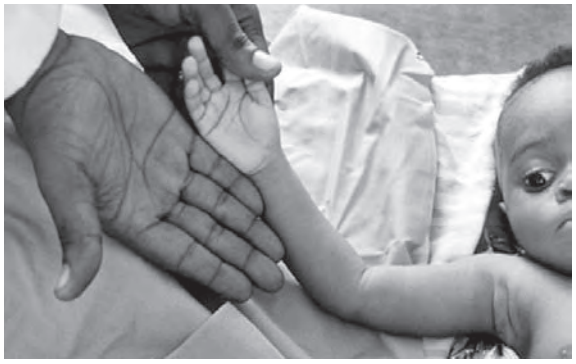

Figure 1: Child with “uncomplicated” severe malarial anaemia

Introduction

Malarial anaemia affects nearly all children in endemic areas and therefore may be considered the most common of all childhood diseases (Fig. 1). There are striking differences in severity, which may range from mild and asymptomatic forms to severe and life-threatening falls in haemoglobin (Hb). The pathogenesis has been shown to include the destruction of parasitized and non-parasitized RBCs and ineffective erythropoiesis. As the relevant data were obtained in relatively small and heterogeneous patient groups, it remained unclear to what extent each of these factors contributes to malarial anaemia and which of them predominates in life-threatening forms.

Severe anaemia is included in the WHO definition of severe and complicated malaria as an Hb of below 50g/L or a haematocrit (Hct) of below 15%. Previous clinical observations indicate that patients with malarial anaemia who have respiratory distress or other additional signs of complicated malaria are at much greater risk of dying than those who have not. The question arises of whether the two forms of severe anaemia differ in pathogenesis, which would be of practical relevance.

Project Description and Results

Parasite drug resistance and severe malarial anaemia

Our studies on the occurrence of severe malaria in conjunction with parasite drug resistance provided evidence for important differences in the development of severe malarial anaemia. Both hospital and community based studies have previously suggested a significant impact of chloroquine (CQ) resistance of the major malaria parasite *Plasmodium falciparum* on malaria mortality. Notwithstanding, CQ remains the most commonly used malaria drug in large parts of sub-Saharan Africa. The CQ-resistance phenotype of *P. falciparum* is closely associated with a T76 mutation of the CQ transporter gene.

We enrolled 189 children diagnosed with severe malaria following the WHO definition. Recorded were the type of malaria complication, the duration of illness, reported previous CQ treatment and the frequency of the T76 P. falciparum genotype. Seventy-seven percent of the patients had detectable CQ in their plasma, and 88% were carrying resistant *P. falciparum*. Significant associations were found (i) between CQ-resistant parasites and plasma CQ levels, (ii) between the presence of CQ in plasma and the reported duration of illness, and (iii) between the reported duration of illness and the occurrence specifically of severe anaemia which was not accompanied by coma, prostration or respiratory distress (Tab. 1). Together these data indicate that *P. falciparum* CQ resistance may promote the development of the form of severe malarial anaemia which is not accompanied by additional complications. This suggests that this form may develop rela0tively slowly, for instance in the course of prolonged parasitaemias due to inefficient treatment attempts. A different form of severe anaemia may develop more rapidly, and this form may cause additional complications including respiratory distress and coma.

	CQ** in plasma	Prolonged illness	„Uncomplicated" severe anaemia
CQ-resistant *P. falciparum*	p=0.001	n.s.***	n.s.
CQ in plasma		p=0.03	n.s.
Prolonged illness	n.s.		p=0.0002

Table 1: Link between CQ-resistant *P. falciparum* and „uncomplicated" severe malarial anaemia

Case reports on the development of severe malarial anaemia

In a longitudinal study designed to assess individual susceptibilities to *P. falciparum* parasitaemias and mild malaria, the development of severe malarial anaemia was monitored in two cases. The study included 450 siblings who were followed over eight months by weekly malaria films and biweekly Hct measurements. Two of these children developed severe malarial anaemia: A 3-year old boy showed a slow Hct decline to 14% over several months, remained asymptomatic, and recovered to an Hct of >30% after antiparasitic treatment; the other one, a 2-year old girl, was hospitalized with an Hct of 11% 11 days after the last study Hct of 30%, received a blood transfusion and antiparasitic treatment, and remained with an Hct of >30% for the remaining two months of the study period. Although there was no hospital documentation on further malaria complications in this case, it might be concluded that, regarding regular weekly consultations by the study physician, the hospital admission must have resulted from acute and severe clinical symptoms. These data suggest that severe malarial anaemia as it is defined comprises at least two clinical entities, which may be termed "uncomplicated" and "complicated" severe anaemia and which may differ in the dynamics of their development and may require different supportive treatments.

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- Evans JA, May J, Tominski D, Eggelte T, Marks F, Abruquah HH, Meyer CG, Timmann C, Agbenyega T, Horstmann RD. **2005**. Extensive pre-treatment with chloroquine and high prevalence of parasite markers of chloroquine resistance in children with severe malaria presenting to a Teaching Hospital in Ghana. QJM 98:789-796.

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- NGFN (German National Genome Research Network)
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Failure to confirm in a large case-control study previously described associations of human genetic variants with pulmonary tuberculosis

Department of Molecular Medicine

Zusammenfassung

Eine genetische Disposition für Tuberkulose wurde in Zwillingsstudien nachgewiesen und zeigt sich daran, dass nur 10% der exponierten Personen erkranken. In früheren Untersuchungen war dies auf Varianten der Gene für Mannose-Binding Protein (*MBL*), Vitamin-D-Rezeptor (*VDR*), Natural Resistance-Associated Macrophage Protein 1 (*NRAMP 1*), Purinergic Receptor P2X (*P2RX7*) sowie Komponenten des Interleukin-1-Gen-Clusters (*IL1a, IL1b*) zurückgeführt worden. In unserer Untersuchung an bis zu 2000 Fall-Kontrollpaaren von HIV-negativen ghanaischen Tuberkulose-Patienten und exponierten, gesunden Vergleichspersonen konnten die Assoziationen mit den beschriebenen Varianten von *MBL, VDR, NRAMP1, P2X7, IL1a* und *IL1b* nicht bestätigt werden. Ebenfalls keine Assoziation fand sich mit Varianten des Gens *Sp110*, das im Mausmodell großen Einfluss auf Resistenz gegen Tuberkulose gezeigt hatte. Allerdings ergaben sich Hinweise auf einen Einfluss der *VDR*- und *MBL*-Varianten in klinischen Untergruppen bzw. mit bestimmten Erregervarianten. Derzeit werden diese Hinweise näher untersucht und eine umfassende Analyse genetischer Varianten von Komponenten der Interferon-γ Signalkaskade durchgeführt.

Project Description and Results

Susceptibility to tuberculosis (TB) has long been known to be strongly influenced by human genetic factors, as indicated by twin studies and the fact that only one out of 10 infected persons falls sick. A limited number of gene variants has, however, so far been reported to be associated with resistance or susceptibility to the disease.

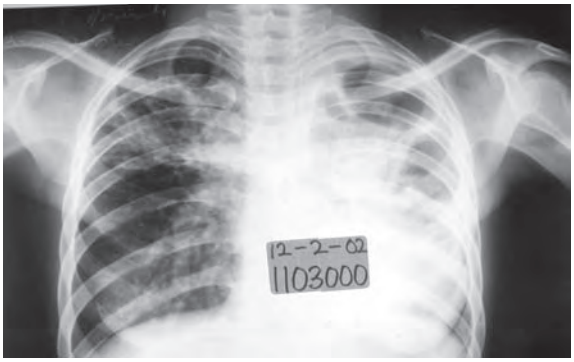

Figure 1: Chest X-ray of a Ghanaian TB patient.

These comprise the genes encoding the natural resistance-associated macrophage protein 1 (*SLC11A1,* formerly *NRAMP1*), mannose-binding lectin (*MBL*), vitamin-D-receptor (*VDR*), purinergic receptor P2X (*P2RX7*), and components of the interleukin-1-gene-cluster (*IL1a, IL1b*). Most of the associations were found in a case-control sample from The Gambia, and some of the associations found have been confirmed or contradicted by other studies.

In order to study genetic variants associated with TB, we have in Ghana collected 2004 HIV-negative patients with newly diagnosed smear-positive pulmonary TB and 2366 unaffected exposed controls. Study participants belonged to the ethnic groups of Akan (Ashanti, Fante, Akuapem), Ga-Adangbe, and groups of northern Ghana (Mole Dagbane, Gurma, Grusi).

Patients were enrolled between September 2001 and July 2004 at Korle Bu Teaching Hospital, Accra, Komfo Anokye Teaching Hospital, Kumasi, and at additional hospitals in Accra, Kumasi, and surrounding districts. Symptoms including cough, hemoptysis, shortness of breath, chest pain, night sweats, fever and weight loss were documented on structured questionnaires. Clinical and laboratory assessments included a physical examination, chest X-ray, two Ziehl/Neelsen-stained sputum smears, culturing of the agents of the *Mycobacterium tuberculosis* complex (*Mtb*) on Löwenstein-Jensen medium, and HIV-1/-2 testing. All cases were treated in the framework of the “Directly Observed Treatment Short-Course Strategy” organized by the Ghanaian National Tuberculosis Programme.

Controls comprised 1117 tuberculin-positive personal contacts, 1120 tuberculin-positive community controls, 114 tuberculin-negative personal contacts and 15 tuberculin-negative community controls. Their characterization included the medical history, clinical examination, chest X-ray, and tuberculin skin tests. Cases and controls were matched for sex and age (± 6 yrs).

Mycobacteria were further characterized by biochemical tests, spoligotyping, DNA fingerprinting and assessment of resistance against the six major drugs used in the treatment ob TB in Ghana.

Human genotyping comprised an intronic and a 3´UTR variant of the *SLC11A1* gene, two promoter and three non-synonymous variants of the *MBL* gene, one synonymous, one non-synonymous and one intronic variant of the *VDR* gene, a non-synonymous and an intronic variant of the *IL1A* and *IL1B* genes, respectively, and a promoter variant of the *P2RX7* gene.

The frequencies of the occurrence of these variants tested were similar among TB cases and controls, and none of the polymorphisms genotyped was associated with either susceptibility or resistance to pulmonary TB in the study group as a whole (Tab. 1). Evidence was found, however, for associations in subgroups formed according to mycobacterial genotypes or tuberculin positivity of controls, which is currently being pursued further.

Table 1: Results in a Ghanaian case-control sample on human genetic variants previously found associated with TB*

gene variant	n, cases/ ctrls	OR	p	p (MH)
SLC11A1_intron	1236/1305	0.94	0.30	0.77
SLC11A1_3´UT	999/1131	1.07	0.83	0.26
MBL_-550	1883/2280	0,89	0.42	0.24
MBL_-221	1899/2286	0.97	0.94	0.72
MBL_rs1800450	1820/1705	0.94	0.81	0.80
MBL_rs1800451	1930/1868	0.83	0.21	0.12
MBL_rs5030737	1820/1704	1.87	0.60	0.66
VDR_rsTaqI	1808/1628	1.03	0.06	0.69
VDR_rsApaI	965/1081	1.10	0.75	0.75
VDR_rsFokI	971/1089	1.07	0.74	0.64
ILA1_rs17561	1673/1254	0.80	0.26	0.09
ILB1_rs1143634	1706/1275	0.79	0.34	0.36
P2RX7_-762	1724/1309	0.87	0.73	0.99

*) Associations were calculated using the χ^2 test, and highest or lowest odds ratios (OR) from comparisons including three genotypes each (wildtype/wildtype, wildtype/mutant, mutant/mutant) are given. MH, p values adjusted for ethnicities using Mantel Haenszel test.

Recently, the murine gene *Ipr1* (intracellular pathogen resistance-1) has been shown to essentially contribute to innate immunity in mouse a model of *M. tuberculosis* infection. When testing for associations of the human homologue of *Ipr1*, *Sp110*, no associations were observed of human TB with 21 *SP110* variants or the resulting haplotypes.

Ongoing studies focus on associations of human genetic variants of components of the interferon-γ receptor signalling pathway. The sample size and the availability of the mycobacterial genotypes will allow for further stratifications with respect to mycobacterial variants and to variants of the other pathway components. Thereby, the analysis will not only address the role of individual components in protection against TB but will, more generally, investigate the potential of a genetic epidemiological approach to trace entire regulatory systems, the use of stratifications for component variants on the sensitivity to identify the influence of others, and the contribution of pathway heterogeneity to the genetic complexity of common diseases.

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- Niemann S, Kubica T, Bange FC, Adjei O, Browne EN, Chinbuah MA, Diel R, Gyapong J, Horstmann RD, Joloba ML, Meyer CG, Mugerwa RD, Okwera A, Osei I, Owusu-Darbo E, Schwander SK, Rüsch-Gerdes S. **2004**. The species *Mycobacterium africanum* in the light of new molecular markers. J Clin Microbiol; 42:3958-62.
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Plasmodium falciparum isolates of placental origin and their expressed *var* gene products

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Zusammenfassung

Schwangerschaftsassoziierte Malaria (PAM) ist ein Hauptgrund für Morbidität und Mortalität bei Neugeborenen und ihren Müttern. Die Immunität gegen PAM entwickelt sich unabhängig von der gegen nicht-PAM. So ist der Schutz, den ein Mensch in der Jugend entwickelt, unwirksam gegen PAM-Parasiten, und es kommt zu einer Anreicherung von Parasiten in der Plazenta. Unsere Untersuchung wichtiger Parasitenantigene und ihrer Interaktionen mit Wirtsrezeptoren dienen dem Verständnis der Malaria Pathogenese und Immunität.

Project Description and Results

The first understanding of PAM was based on the observation that placental isolates adhered to the glycosaminoglycan chondroitin sulphate A (CSA). Efforts to identify the molecules mediating this adhesion have led to the identification of two *var* genes encoding structurally unrelated PfEMP-1 molecules with CSA-binding domains, but their role remains controversial. To closely mimic the process of adhesion in the placenta, we emphasised the study of *var* genes (named *var*PAM) expressed by *P. falciparum* infected erythrocytes (IE) collected ex-vivo from placentas. These parasites expressed distinct DBL-γ sequence types capable of binding CSA (Khattab et al, JID 2001, 2003). To examine *var*PAM genotypes and phenotypes, a partial DBL-γ sequence from parasite isolate 732 formed the basis for cloning the full-length 732 *var*PAM gene. Recombinant 732 DBL-γ domain derived therefrom showed CSA-binding properties, and anti-732 DBL-γ antibodies blocked IE binding to CSA. In contrast, no CSA-binding or anti-adhesion activities were observed for the other domains of the 732 *var*PAM gene. Further, antibodies in human plasma that react with recombinant 732 DBL-γ protein correlated with reduced placental parasite density (Figure 1), showing for the first time a link of a single PfEMP-1 domain with immune control of placental parasitaemia. By flow cytometry, antibodies in human plasma recognise the panel of placental isolates in a parity- and sex-dependent manner. The isolates were also found capable of binding additional receptors, such as non-immune IgG and IgM, even though their role in sequestration is not yet known. The discovery that other receptor molecules are involved in placental adhesion has important implications in the race to find a PAM vaccine with the appropriate anti-adhesive characteristics.

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- Yu Shan Chia

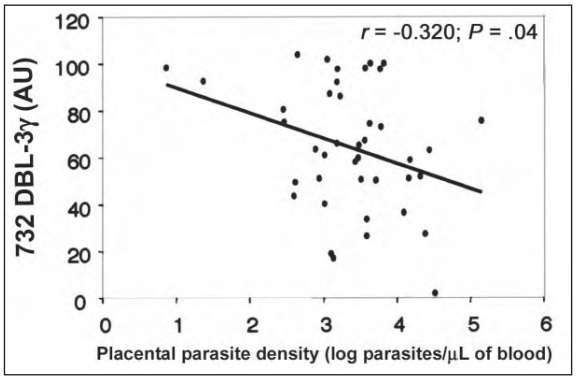

Figure 1: Correlation between antibody levels to recombinant DBL-γ and placental parasite density.

Intermittent treatment with Sulfadoxine-Pyrimethamine in African children as a means of malaria control

Research Group Infection Epidemiology

Zusammenfassung

Seit Januar 2003 findet eine kontrollierte klinische Studie mit 1070 Teilnehmern statt, die die Wirksamkeit einer intermittierenden präventiven Malariabehandlung von Kleinkindern (IPTi) auf die Verhinderung von Malariaattacken und Episoden schwerer Anämie untersucht. Die Behandlung wurde im Rahmen der Routineimpftermine der WHO (EPI) verabreicht. Ziel der Studie ist es, die Effizienz eines modifizierten IPTi-Schemas in einem holoendemischen Gebiet in der Ashanti-Region in Ghana zu untersuchen. Das Projekt umfasst auch Studien zur Epidemiologie und Dynamik natürlicher *Plasmodium-falciparum*-Infektionen im Kleinkindalter und von parasitären Medikamentenresistenz-Markern.

Introduction

There is an urgent need for available and affordable strategies to control malaria morbidity in African children. It has been shown that antimalarial chemoprophylaxis is potentially capable to reduce malaria morbidity, school absenteeism, and all-cause mortality. However, continuous chemoprophylaxis in the first years of life can also result in the loss or delay of acquired immunity which can lead to a „rebound“ of the risk of severe malaria.

In a recent trial on intermittent treatment with Sulfadoxine-Pyrimethamine (SP) at 2, 3, and 9 months of age (IPTi), the rate of clinical malaria during the first 12 months of life was significantly reduced and no rebound effects were observed. This study has indicated that the intermittent application of SP is safe and has beneficial effects for the children. A major concern of a mass treatment strategy with anti-malarial drugs is the development of drug resistance which is not yet investigated in detail for the IPTi approach.

Project Description and Results

A double-blinded, randomized, placebo-controlled trial was conducted in nine neighbouring villages of the Afigya Sekyere district in the Ashanti Region, Ghana. Infants aged three months were recruited from January to December 2003 and the study was completed in September 2005. The intervention comprised one dose of SP or placebo at months 3, 9, and 15 of life in 1070 children. The follow-up period was 21 months with passive case detection and monthly active visits.

In order to define the effectiveness of the intervention the following parameters have been or will be analysed: i) the level of protection from malaria attacks during the treatment period, ii) the effect on malaria morbidity after suspending treatment, iii) the influence of the intervention on the development of drug resistances, iv) the impact of the intervention on the development of immunity, v) the possible influence of the intervention on sub-clinical organ dysfunction due to chronic *Plasmodium falciparum* infection.

In an epidemiological survey the prevalence and multiplicity of *P. falciparum* infections (MOI) were assessed in the study population at the third month of life (Fig. 1). The occurrence of early infections was dependent on the season (month-stratified prevalence 6.4% – 29.0%). Diversity of msp-alleles was extensive and significantly higher in the dry than in the rainy season. The level of infection prevalence and the high MOI identified (median 4, maximum 15 strains per isolate) in the first months of life indicate early contacts with parasites exhibiting a wide repertoire of antigens and, most likely, multiple infections per single mosquito bite.

In order to assess the prophylactic efficacy of a single SP dose and to determine the occurring patterns of SP resistance after drug application, 63 aparasitemic and afebrile children at the age of nine months were enrolled in a clinical sub-study with weekly follow-ups. The interval between enrolment and the first *P. falciparum* infection was slightly delayed during the first weeks in children who had received SP (Fig. 2A). After week nine, the time-dependent proportion of parasitemic children tended to be higher in the treatment group for a short period of time. The incidence rate of *P. falciparum* infections was 3.5 per person-year in children treated with SP and 2.2 in the placebo group (incidence rate ratio [IRR] 1.6, 95% confidence interval [CI] 0.9-2.8, n.s.). The period between treatment and the first detection of *P. falciparum* isolates with four resistance-associated mutations was shorter in children who had received SP ($p<0.05$) (Fig. 2B). Differences became apparent after week eight, whereby the relative rate for the incidence of isolates with four mutations was two times higher in the treatment than in the placebo group (treatment group 2.7, placebo group 1.3, IRR 2.1 [CI 1.0-4.3], $p<0.05$).

Apparently, three consecutive phases differentially influence infection dynamics after SP application. Firstly, during the period of high drug levels, reinfections with sensitive and partly resistant isolates are delayed. Thereafter, during a limited phase after complete drug elimination, the rebound becomes apparent with a sharp increase of infections with fourfold mutations. After this short rebound phase, a similar increase of the proportion of infected children can be observed in both groups.

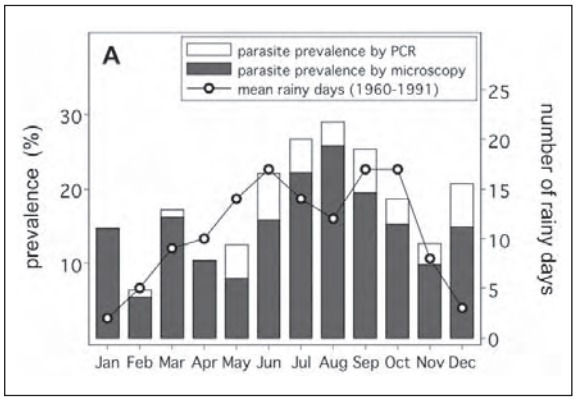

Figure 1: Month-stratified *P. falciparum* prevalence assessed by conventional microscopy (black bars) and by PCR (white bars). The mean number of rainy days per month (hollow circle).

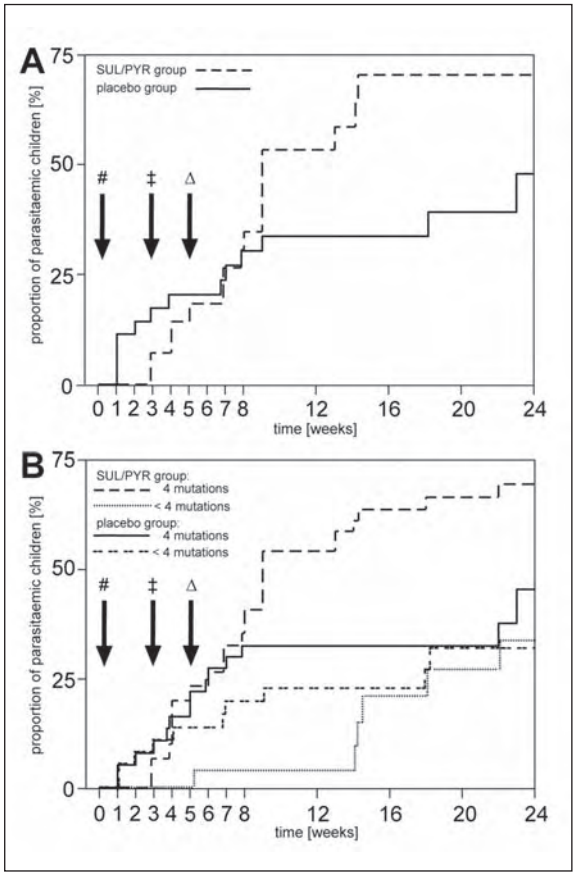

Figure 2:

A) First PCR-based detection of *P. falciparum* parasitemia in the SUL/PYR and in the placebo group;

B) First occurrence of isolates exhibiting four pfdhfr/pfdhps mutations of *P. falciparum* and variants with less than four mutations in both treatment groups.

#, application of either SUL/PYR or placebo;

‡, approximate elimination of PYR (five half-life cycles);

Δ, complete elimination of SUL.

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- Kobbe R, Marks F, May J, Meyer CG. **2005**. Antifolates in prevention of HIV-associated opportunistic infections and in intermittent preventive treatment of malaria in Africa. Trop Med Int Health 10:1-2.
- Marks F, von Kalckreuth, Kobbe R, Adjei S, Adjei O, Horstmann RD, Meyer CG, May J. **2005**. Rebound effects and emergence of *Plasmodium falciparum* pyrimethamine resistance by single dose sulfadoxine-pyrimethamine. J Inf Dis 192:1962-5.
- Evans JA, May J, Tominski D, Eggelte T, Marks F, Abruquah HH, Meyer CG, Timmann C, Agbenyega T, Horstmann RD. **2005**. Pre-treatment with chloroquine and parasite chloroquine resistance in Ghanaian children with severe malaria. QJM 98:789-96
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- Kobbe R, Neuhoff, Marks F, Adjei S, Adjei O, Horstmann RD, Meyer CG, May J. Seasonal dynamics of *Plasmodium falciparum* prevlence and high parasite diversity of first infections in infants from central Ghana, West Africa. Trop Med Int Health: in press.

Funding

- BMBF (German Federal Ministry of Education and Research)
- Volkswagen Stiftung
- DAAD (German Academic Exchange Service)
- Vereinigung der Freunde des Tropeninstituts Hamburg e.V.

Cooperating Partners

- Dept. Human Parasitology, Institute for Tropical Medicine, Eberhard Karls University Tübingen
- Institute for Tropical Medicine Berlin
- Division of Infectious Diseases, Tropical Medicine & AIDS, Academic Hospital, Amsterdam, The Netherlands
- Kumasi Centre for Collaborative Research (KCCR), Ghana

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- Samuel Adjei
- Wibke Busch
- Robin Kobbe
- Christina Kreuzfeld
- Florian Marks
- Nadine Schreiber

Persistence of HIV-1 structural proteins and glycoproteins in lymph nodes of patients under HAART

Department of Pathology and Körber Laboratory for AIDS Research

Zusammenfassung

Bei der HIV-Infektion sind sowohl die zellvermittelte wie auch die humorale Immunantwort in Mitleidenschaft gezogen. Eine komplette Normalisierung dieser komplexen Immunschwäche ist bei der Mehrzahl der infizierten Personen auch durch Langzeittherapie, die in der Lage ist, die Virusvermehrung für lange Zeit unter die Nachweisgrenze zu drücken, nicht zu erzielen. Bei der humoralen Immunantwort spielen die follikulären dendritischen Zellen (FDC) der Keimzentren in den sekundären lymphatischen Organen eine wichtige Rolle. Bei der HIV-Infektion stellen sie ein sehr wichtiges Virusreservoir dar, weil FDC das Virus binden und für lange Zeit an der Zelloberfläche lagern. Wir haben den Effekt der antiretroviralen Therapie auf dieses Virusreservoir untersucht. Bei Patienten, die auf Therapie gut ansprachen (Viruslast im Plasma <25 RNA Kopien/ml) ist HIV RNA in den Keimzentren nicht nachweisbar. Demgegenüber sind bei allen untersuchten Fällen p24 und p17 Proteine sowie das Glykoprotein gp120/gp41 des HIV-1 an der Oberfläche der FDC nachzuweisen. Da die Viruslast für Monate unter der Nachweisgrenze lag, konnten die Strukturproteine nur vor dem Beginn der Therapie in die Keimzentren gelangen. Eine der Konsequenzen dieser Antigenpersistenz könnte sein, dass die Patienten Antikörper gegen „historische" HIV-Varianten bilden und das Auftreten neuer Virusvarianten begünstigen.

Introduction

The infection with HIV-1 is characterised by a severe impairment of both cellular and humoral immunity. The alteration of the B cell compartment is manifested by hypergammaglobulinemia, increased spontaneous antibody secretion in vitro, enhanced levels of autoantibodies and decreased humoral responses to antigens. In addition, the incidence of B cell lymphomas is also increased. Since the introduction of highly active antiretroviral therapy (HAART) the infection has been efficiently controlled in a large number of patients for years, nevertheless, the reversal of the profound alterations of the T and B cell compartments of the immune system is slow and incomplete. Several mechanisms have been suggested for the excessive B cell activation including the direct stimulatory effects of HIV structural proteins and glycoproteins on these cells. Earlier investigations documented that in chronically infected untreated individuals the capsid protein p24 as well as the matrix protein p17 of HIV-1 are deposited on the surface of follicular dendritic cells (FDC) of the germinal centres (GC) in the secondary lymphoid tissue (Tenner-Racz et al. 1986, Am J Pathol 123:9). Since FDC-bound antigens play a crucial role in the humoral immune response we have analysed the influence of HAART on the amounts of these proteins and the glycoprotein gp120/gp41 in the GC.

Project Description and Results

We have selected 7 cases from clinical trials according to the following criteria: (i) availability of lymph node biopsies both before the initiation of HAART and during therapy when plasma viremia exhibited <25 RNA copies / mL for at least 6 months; (ii) the presence of a marked follicular hyperplasia (FH) at the baseline; and (iii) the follow-up biopsies should show the persistence of FH in some patients and normalisation of the follicles in others. Detection of HIV-1 RNA in the lymph nodes was performed by in situ hybridisation on paraffin sections. Antibodies against HIV proteins p17 and p24 as well as glycoprotein gp120 / gp41 were applied on frozen sections and visualised by the alkaline phosphatase anti-alkaline phosphatase reaction. In addition, we monitored HIV-1 RNA in the plasma, antibodies to HIV-1p17, HIV-1p24 and HIV-1env by ELISA. Neutralisation of R5 and X4 HIV-1 was also tested. The *in situ* hybridisation revealed high amounts of FDC-bound HIV RNA in all lymph nodes removed prior to therapy. The frequency of HIV RNA-producing cells varied between 0.7 and 3.7 per mm^2 of tissue section. This contrasted sharply with the follow-up biopsies in which FDC-bound HIV RNA was under the limit of detection and productively infected cells were very rare (0 – 0.005 cells per mm^2 of

tissue). In contrast, HIV structural proteins and glycoproteins were always present in the GC of the follow-up biopsies (Fig 1), even in cases that showed remission of the FH. It is likely that these antigens were deposited on FDC before the initiation of HAART since in all patients the virus burden in the plasma was constantly below the limit of detection for at least 6 months. Thus, HIV antigen can not be captured from the blood circulation. It is also unlikely that the very few productively infected cells that were present in these lymph nodes provided the amounts of HIV proteins that could replenish the FDC antigen pool. Thus, the GC positive for HIV antigens are long-lived where p17, p24 and gp120 / gp14 persist for a long time. Specific antibody responses to these HIV antigens, as evaluated by ELISA and virus neutralisation, also persisted. Experimental data suggest that FDC-bound viral antigens in long-lived GC most probably are involved in the maintenance of serological IgG memory (Bachmann 1998 Immunol Rev 17:329). Thus, in our cases the persisting humoral responses to HIV antigens very likely represent “conserved” antibodies generated and maintained by FDC antigenic pool established before virus replication was suppressed by HAART. Consequently, this “conserved” humoral response could provide an advantage for the emergence of new virus variants that are resistant to the “historical” antibodies.

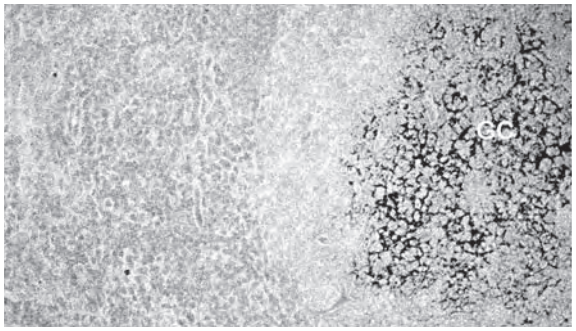

Figure 1: Persistence of the capsid p24 protein (black) in a germinal centre (GC) under HAART. Original magnification: 80x

Selected Publications

- Popovic M, Tenner-Racz K, Pelser C, Stellbrink HJ, van Lunzen J, Lewis G, Kalyanaraman VS, Gallo RC, Racz P. **2005**. Persistence of HIV-1 structural proteins and glycoproteins in lymph nodes of patients under HAART. Proc Natl Acad Sci USA 102:14807-14812
- Mehandru S, Tenner-Racz K, Racz P and Martin Markowitz. **2005**. The gastrointestinal tract is critical to the pathogenesis of acute HIV-1 infection. J Allergy Clin Immunol 116:419-422
- Schmitz JE, Johnson RP, McClure HM, Manson KH, Wyand MS, Kuroda MJ, Lifton MA, Khunkhun RS, McEvers KJ, Gillis J, Piatak M, Lifson JD, Grosschupff G, Racz P, Klara Tenner-Racz K, Rieber EP, Kuus-Reichel K, Gelman RS, Letvin NL, Montefiori DC, Ruprecht RM, Desrosiers RC, and Reimann KA. **2005**. Effect of CD8+ lymphocyte depletion on virus containment after simian immunodeficiency virus SIVmac251 challenge of live attenuated SIVmac239{delta}3-vaccinated rhesus macaques. J Virol. 79:8131-8141.
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- Gerstner AO, Trumpfheller C, Racz P, Osmancik P, Tenner-Racz K and Tarnok A. **2004**. Quantitative histology by multicolor slide-based cytometry. Cytometry 59A: 210-219

Funding

- BMBF (Federal Ministry of Education and Research)

Cooperating Partners

- Mikulas Popovic, Robert C. Gallo, Gorge Lewis from the Institute of Human Virology, University of Maryland, Baltimore, MD, USA
- Hans-Juergen Stellbrink, Jan van Lunzen, University Medical Centre Hamburg-Eppendorf

Investigators

- Paul Racz
- Klara Tenner-Racz

Report on KCCR Activities

Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) Kumasi, Ghana

The institute settled down in the new environment on the premises of Kwame Nkrumah University of Science and Technology (KNUST) in November 2003 after spending six years of pioneering work at the KNUST School of Medical Sciences (SMS). KCCR is becoming increasingly attractive with its newly equipped laboratories, car park, accommodation, and catering facilities. KCCR was nominated in line with the restructuring of KNUST to be the Research Centre of the newly established College of Health Sciences. KCCR was also nominated in 2005 to be a WHO-recognized Buruli ulcer reference laboratory for the northern zone of Ghana.

KCCR has a permanent staff strength of 42 and other support staff including medical officers, scientists, and nurses. The main laboratory of KCCR on KNUST Campus became a base for various projects. For the handling of highly infectious material containing mycobacteria (Buruli, Tuberculosis) and HIV a bacteriology L2 and a basic BSL3 laboratory are available. Apart from the main laboratories in Kumasi, KCCR is maintaining its laboratories at the Presbyterian Health Service Hospital in Agogo (PHS) for its malaria and Buruli ulcer projects as well as in Dunkwa (Upper Denkyria District) for onchocerciasis and Essiama (Nzema East, Western Region) for *Wuchereria bancrofti* research.

KCCR also maintained its close collaboration with the Department of Child Health at the Komfo Anokye Teaching Hospital Kumasi (KATH), where it participates in the running of projects in severe malaria. The scope of KCCR research activities widened with the inclusion of ecological factors of diseases. Currently, projects at KCCR cover the following areas:

- The genetic factors of susceptibility and resistance to malaria and tuberculosis
- Intermittent treatment of malaria in children
- Chemotherapy and clinical aspects of filariasis.
- Vaccine candidates in onchocerciasis
- Transmission of malaria and filariasis
- Diagnostics and environmental studies in Buruli ulcer
- Health impact of Aflatoxin ingestion

Funding of running programmes was mainly obtained from the European Commission, the German National Genome Research Network (NGFN) the German Malaria Initiative and Volkswagen Stiftung.

The success of research programmes is also reflected in direct benefit for the population of Ghana. This is in respect to various malaria programmes, successfully addressing the ecology of malaria and

KCCR offers 300 m^2 of research laboratory space, well equipped with biosafety hoods, thermocyclers, electrophoresis units, microscops and a flow cytometer.

Die 300 m^2 Laborfläche am KCCR sind ausgestattet mit Sterilwerkbänken, PCR-Geräten, Gelelektrophorese-Einheiten, Mikroskopen und einem Durchflusszytometer.

management of severe malaria. The KCCR treatment programmes in onchocerciasis and elephantiasis shorten the ten-year and more treatment duration to six weeks for those living out of the transmission zone. This new findings could be integrated in the national programmes and aim at the eradication of the diseases. The Buruli ulcer programme with its emphasis on early detection is aiming to avoid long lasting hospital admission with an average of three months. When research records from KCCR indicated more than 30% resistance to the commonly recommended Tuberculosis treatment schemes in more than 3000 cases the Ministry of Health of Ghana changed the drug policy by replacing Streptomycin with Ethambutol. Treatment duration could be shortened by this change from 8 to 6 months.

KCCR is building up more capacity in malaria research together with SMS, KATH Agogo Hospital and Partners outside Ghana. Studies on severe malaria are planned to continue with participation in a multi centre study, funded by the Wellcome Trust to compare the use of artesunate with quinine in severe malaria. The study is due to start in the first half of 2006.

A research group comprising members of KCCR, the SMS, Department of Child Health at KATH, and Agogo Presbyterian Hospital, made a successful application to the GlaxoSmithKline/Malaria Vaccine Initiative (GSK/MVI) consortium to develop a vaccine study site. This site, one of eight throughout Africa was selected following a site visit in February 2005. Preliminary discussions are ongoing with a view to starting the studies during the first half of 2006. New programmes on diagnostics and treatment of Buruli ulcer and onchocerciasis funded by Volkswagen and EU respectively will start early 2006 and these will be a continuation to the previous programmes.

KCCR is also aiming at capacity building for its own staff. It is supporting 12 students for their postgraduate training. The first KCCR PhD student and two Masters students successfully defended their theses. Another PhD student is currently finalizing his work at the University of Bonn and one medical doctor is conducting a two-year DAAD sponsored programme at the BNITM in Hamburg.

KCCR offered training courses for Biological Science and Biochemistry students from the College of Science at KNUST, including practical sessions on molecular biology topics. Instrumental for all training activities was the Head of KCCR Laboratories who was sponsored by the German Centre for International Migration and Development (CIM).

KCCR also profited enormously from the input of the Senior Expert Service Programme of DAAD, when among others Prof. Garms as a renowned entomologist visited KCCR twice and supported students in the organization of their scientific work. Apart from this KCCR organized seminars and workshops in Kumasi and Accra.

We are most grateful to our partners in Ghana and outside Ghana, specifically Bernhard Nocht Institute for Tropical Medicine and friends for their support and interest in the development of KCCR.

Thomas Kruppa, Director KCCR

Bericht über die Aktivitäten des KCCR

Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) Kumasi, Ghana

Das *Kumasi Centre for Collaborative Research in Tropical Medicine*, gegründet 1997, ist seit 2003 in eigenen Gebäuden auf dem Campus der Universität ansässig. Ausgerüstet mit modernen Laboren, Gästehaus, Kantine und Fahrzeugen, wird das KCCR als Standort für Tropenmedizin an der örtlichen *Kwame Nkrumah University for Science and Technology* (KNUST) zunehmend attraktiver. Im Laufe der Umstrukturierung der Universität wurde das KCCR auf Grund der engen Verbindung zur medizinischen Hochschule zum Forschungszentrum des *College of Health Science* ernannt. Erfolgreiche Forschungsarbeiten zu Buruli ulcer, begonnen in 2002, führten dazu, dass das KCCR 2005 von der WHO offiziell zum nationalen Referenzlabor für Buruli ulcer ernannt wurde. Gegenwärtig beschäftigt das Institut neben 42 Angestellten eine wechselnde Anzahl von temporär in Projekten tätigen Mitarbeiten, darunter Ärzte und Krankenschwestern.

In den Laboratorien des KCCR wurden molekularbiologische Tests etabliert und Mykobakterien in der Bakteriologie erfolgreich gezüchtet. Zur weiteren Bearbeitung dieser hochinfektiösen Bakterien, wie auch für Arbeiten mit HIV Viren, steht ein Labor der biologischen Sicherheitsstufe drei zur Verfügung. Neben den Laboratorien in Kumasi unterhält das KCCR Laboratorien im *Presbyterian Health Service Hospital* in Agogo (Krankenhaus PHS Agogo) für Forschungen über Malaria und Buruli ulcer, im Distrikt Hospital von Dunkwa (Upper Denkyria District, Central Region) für Onchozerkose und Buruli ulcer und in Essiama (Nzema East District, Western Region) für Arbeiten über Filariasis. Ferner arbeitet das KCCR mit der Abteilung Pädiatrie im Komfo Anokye Teaching Hospital (KATH), dem Lehrkrankenhaus der Universität von Kumasi zusammen und führt gemeinsame Projekte zur schweren Malaria durch. Die Forschungsarbeiten zur Malaria, Filariasis und Buruli ulcer finden ihre Ergänzung durch Übertragungsstudien und der Einbeziehung ökologischer Faktoren. Folgende Themen werden gegenwärtig im KCCR bearbeitet:

- Genetische Arbeiten zur Empfänglichkeit und Resistenz bei Malaria und Tuberkulose
- Optimierung der Diagnostik von Buruli ulcer und Tuberkulose
- Klinische Untersuchungen und Prophylaxe der Malaria im frühen Kindesalter
- Chemotherapie von Onchozerkose und Elephantiasis
- Testung von Impfstoffkandidaten bei Onchozerkose
- Studien zur Übertragung der Malaria und Elephantiasis
- Auswirkungen der Aflatoxinaufnahme, Nahrungsmittelbelastung und Bodenuntersuchungen.

Der KCCR-Campus ist im Technologiepark der Kwame Nkrumah Universität von Kumasi angesiedelt. Auf dem Campus stehen neben modern ausgestatteten Laboratorien auch ein Gästehaus, ein großer Seminarraum und eine Werkstatt zur Verfügung.

The campus of KCCR is located in the science park of Kwame Nkrumah University campus. KCCR comprises modern laboratories, a seminar room, vehicle maintenance and a guesthouse.

Diese Programme wurden im Wesentlichen durch Fördermittel der Europäischen Kommission, des deutschen Nationalen Humangenomprojekts (NGFN), der Deutschen Malarainitiative und der Volkwagenstiftung ermöglicht.

Die gewonnen Erkenntnisse kommen der Bevölkerung direkt zu Gute. Als Beispiele zu nennen sind die verbesserte Behandlung von schwerer Malaria, kürzere Behandlungszeiten für Elephantiasis- und Onchozerkosepatienten außerhalb der Endemiezone, die Früherkennung von Buruli ulcer Geschwüren und eine Änderung der nationalen Richtlinie zur Behandlung von Tuberkulosepatienten.

Die erfolgreiche Zusammenarbeit auf dem Gebiet der Malaria mit der *School of Medical Sciences* (SMS), KATH, Krankenhaus PHS Agogo und auswärtigen Partnern hat sich bewährt und wird ausgebaut. In Planung ist eine gleichzeitig in mehreren Ländern durchgeführte und durch den Wellcome Trust geförderte Studie, um die Wirkung zweier Medikamente (Artesunate und Chinin) bei schwerer Malaria zu vergleichen. Das Malaria-Genomforschungsprogramm wird in 2006 ebenfalls multizentrisch fortgeführt Das KCCR war federführend bei der inzwischen erfolgreichen Bewerbung zur Testung der ersten Malariavakzine des Glaxo Smith Kline/ Malaria Vaccine Initiative (GSK/MVI) Konsortiums. Das Krankenhaus PHS Agogo wird gegenwärtig als Impfstofftestzentrum vorbereitet. Der Studienbeginn dieser in 8 afrikanischen Zentren anlaufenden Testreihe ist für Mitte 2006 geplant. Diese positive Entwicklung wird nachhaltig die zukünftige Malariaforschung des KCCR beeinflussen.

Weiteres Ziel des KCCR ist die Ausbildung des eigenen Personals und des – gegenwärtig aus 12 Studenten bestehenden – wissenschaftlichen Nachwuchses. Der erste KCCR-Kandidat schloss erfolgreich seine Promotion im Fachbereich Biologie ab, ein weiterer beendet derzeit den praktischen Teil seiner Doktorarbeit an der Universität Bonn und wird 2006 zurück erwartet, um seine Arbeit in der gleichen Fakultät einzureichen. Ein ghanaischer Arzt absolviert im BNI eine zweijährige molekulargenetische Grundausbildung. Diese Studienaufenthalte wurden durch den DAAD ermöglicht. Masterstudenten des KCCR profitierten weiterhin von der Betreuung durch erfahrene Wissenschaftler, darunter Professor Garms (BNI), deren Anleitung zum wissenschaftlichen Arbeiten sowohl im Feld als auch im Labor durch das Senior Expert Service Programm (SES) des DAAD ermöglicht wurden. Das KCCR veranstaltete Kurse in Theorie und Praxis der Molekularbiologie für Studenten der Biologie und Biochemie (*College of Science* der KNUST). Diese Kurse werden zukünftig auch Labormedizinstudenten des *College of Health Science* angeboten. Federführend ist hier der Laborleiter des KCCR, der aus Fördermitteln des Centrums für Internationale Migration und Entwicklung (CIM) in Frankfurt/Main finanziert wird. Die Verlängerung der Stelle um weitere zwei Jahre ab 2006 wurde genehmigt und durch die finanzielle Beteiligung des BNI ermöglicht.

Das KCCR ist allen Partnern in Ghana und außerhalb Ghanas, besonders dem BNI für ihr Interesse an der Entwicklung des KCCR zu Dank verpflichtet.

Thomas Kruppa, Direktor KCCR

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Kumasi, Ghana

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- Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana
- St. Georges Hospital Medical School, London
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Use of insecticide-treated nets to protect cattle against insects of veterinary and medical importance in Ghana

Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR)
Kumasi, Ghana

Zusammenfassung

Bei einer in Kenia durchgeführten Untersuchung konnten Milchkühe durch Umzäunung der Stallungen mit Insektizid behandelten Polyesternetzen (Höhe 150 cm) wirksam gegen Tsetsefliegen und Übertragung von Trypanosomen geschützt werden (Bauer et al., 2006). Außerdem deutete sich an, dass in der Umgebung der Stallungen die Belästigung durch Fliegen und Stechmücken merklich zurückging. Diese Beobachtungen sollten auf dem Gelände der Rinderfarm der Universität Kumasi im Waldgebiet Ghanas in einem Pilotversuch überprüft werden, und es sollte untersucht werden, ob solche Netze zum Schutz gegen human- und veterinärmedizinisch wichtige Insekten zum Einsatz kommen können. Ein mit zwei Zebubullen besetzter Versuchsstall (6 m x 7 m, Fig. 1) wurde mit einem mit Deltamethrin imprägniertem Polyesternetz (Höhe 100 cm) umzäunt und der Anflug medizinisch wichtiger Insekten über einen Zeitraum von sechs Wochen gemessen (Anflug von Stechmücken an Menschen, Einflug von Fliegen in monokonische Fallen, Fang Blut saugender Mücken in mit Duftstoffen versehenen Mückenfallen). Als Kontrollen dienten drei weitere Ställe: ohne Netz mit Zebubullen, Netz ohne Imprägnierung mit Zebubullen, ohne Netz ohne Zebubullen. In dem mit Insektizidnetz geschütztem Stall wurden deutlich weniger medizinisch und veterinärmedizinisch wichtige Insekten gefangen als in den Kontrollstallungen.

Introduction

The successful protection of dairy cattle in Kenya with a 150 cm high fence of insecticide-treated mosquito netting (Bauer et al., 2006) against tsetse-transmitted trypanosomosis inspired a pilot trial near Kumasi, in the forest zone of Ghana. Observations of the participating farmers during the first trial in Kenya had also indicated a reduction of the mosquito populations. This time, a deltamethrin-treated fence of 100 cm height was tested for its potential to protect cattle against mosquitoes, biting and nuisance flies of veterinary and medical relevance. In areas of high densities of these insects the use of nets may have additional human health benefits by controlling vectors of diseases, such as sleeping sickness, malaria or leishmaniasis.

Project Description and Results

The trial site was the cattle research farm of the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana; N 6° 41'; W 1° 32'. Four identical experimental pens A, B, C and D (Fig. 1) each measuring 6 m x 7 m were constructed at a distance of about 500 m from each other in locations with similar vegetation. Half of each pen was covered with corrugated iron sheets. Chicken wire at a height of 100 cm to protect the nets surrounded each pen.

Pen A served as control without net and animals; B was protected with an untreated net; C had no net and D was protected with the deltamethrin treated net (polyester, 25 holes/inch^2, height 100 cm). B, C and D had two zebu bulls which were rotated between the three pens at weekly intervals. Effects of the treated netting on fly and mosquito populations were compared at weekly intervals during six weeks in October and November 2005.

Human landing catches were carried out once a week from 6pm to 6am (12 h) within and 20 m outside the four pens. Fourteen mono-conical traps developed to catch tsetse flies and other nuisance insects were placed 20 to 30 m away from the four pens and at watering places between the pens. Four odour-baited battery-driven mosquito traps designed to catch anthropophilic mosquitoes (BG-Sentinel® Mosquito Traps, BioGents GmbH, Regensburg) were operated within the four pens once a week from dusk to dawn (12 h) a day before the human landing catches. Digital pictures of all animals were taken twice per week in order to count and compare the number of nuisance insects for each bull.

Main results are summarized in Table 1. Two *Anopheles* species were caught on human bait, *A. gambiae* (probably sensu stricto), which is the main vector of malaria in the area, and *A. ziemanni*, which generally is regarded as zoophilic. The monthly biting rate (MBR) of 140 estimated for *A. gambiae* inside the protected pen D was about 60% of that of B and C (255 and 210, resp., both with cattle), but only 23% of that of A (605, without cattle). Examination of *A. gambiae* and *A. ziemanni* for infections with *Plasmodium* spp. by using ELISA tests are in progress. Numbers of Culicinae (*Culex* spp., *Mansonia* spp.) caught inside pen D were about 31% of that of A, B and C.

Table 1: Total numbers of insects caught on human bait, in mono-conical traps and mosquito traps.
A control pen, no net, no animals;
B with two zebus, protected with untreated net;
C two zebus, no net;
D two zebus, protected with treated net.

Pens		A	B	C	D
Human landing catch					
Anopheles gambiae s.l.	Inside	121	51	42	28
	Outside	31	37	45	33
Anopheles ziemanni	Inside	18	57	28	32
	Outside	175	125	117	77
Culicinae	Inside	379	514	348	128
	Outside	520	650	405	321
Mono-conical traps (outside pens)					
Muscinae		65	389	498	37
Stomoxyinae		16	599	587	27
Tabanidae		7	6	3	5
Mosquito traps (inside pens)*					
Anopheles	*gambiae*	3	4	1	4
	ziemanni	1	4	10	6
Culicinae		127	388	266	128
Ceratopogonidae		0	1529	817	441
Phlebotominae		112	389	260	171

* Mosquito traps were operated for only 4 nights in Pen A instead of 6 nights in Pens B, C and D.

The majority of insects caught by the mono-conical traps were Muscinae and Stomoxyinae (house and stable flies). A strong increase of the catches observed near pens B and C during weeks three and four may be attributed to the excellent breeding conditions in cow dung and remnants of fodder, which were regularly removed from the pens and deposited nearby. Fly densities did not increase at the protected pen D, where numbers of Stomoxyinae only reached 4.6% of that of B and C. Very few flies were caught near A, where no cows were kept (2.7% of B and C). Evaluation of digital photographs of selected body parts showed significantly fewer biting and nuisance flies per zebu in pen D (14.1) than in B (47.2) and C (49.7). The untreated net of pen B was not an effective physical barrier for the flies. No tsetse flies were caught indicating their low density or even absence in the study area.

The odour-baited mosquito traps turned out to be less efficient than the human landing catch. They mainly attracted Culicines, but only few *Anopheles*. However the traps provided useful information on Ceratopogonidae (biting midges) and Phlebotominae (sandflies), both of relevance in human and veterinary medicine.
Clear effects of the insecticide-treated fence were recorded for almost all groups of insects, but results differed depending on the catching method. Irritation of cattle by high numbers of flies and mosquitoes may affect productivity leading to lower weight gains or milk yields. Protecting livestock therefore not only reduces disease transmission but also increases animal production and income. Considering the importance of nuisance and biting flies the use of insecticide-treated fences is likely to have far-reaching benefits for livestock keepers and pastoral communities. Further experiments will be necessary to investigate the potential of insecticide-treated fences as an efficient protection against vectors of medical importance.

Selected Publications

- Bauer B et al. **2006**. Evaluation of a preliminary trial to protect zero-grazed dairy cattle with insecticide-treated mosquito netting in Western Kenya. Trop. Anim. Hlth and Prod., 38, 1, 29 – 34.

Funding

- Vestergaard Frandsen/AS, Kolding, Denmark, Lausanne, Switzerland

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- Jürgen May, Rolf Garms, BNI

Figure 1: Experimental pen with two zebus protected with deltamethrin treated net.

Clinical Department

Klinische Abteilung

Clinical Department

Department Head´s Summary

In 2005, the Clinical Department of Bernhard-Nocht-Institute for Tropical Medicine consisted of the patient-admitting wards, an outpatient department for tropical diseases, a Centre for Travel Advice and a clinical research group. Main emphasis is on patient care, in addition work comprises counselling of hospital doctors and general practitioners all over Germany in cases of complicated differential diagnoses and therapeutical problems, travel advice and vaccinations, training and continued medical education of students, specialised medical staff and doctors as well as in clinical research. In the scope of epidemic control, the Clinical Department is the first contact in cases of highly contagious diseases. As of January 1st, 2006, the Clinical Department has been integrated into the University Medical Centre Hamburg-Eppendorf (UKE) as newly founded independent "Section for Tropical Medicine" (Part of the Centre I for Internal Medicine). The outpatient department for tropical diseases as well as the Centre for Travel Advice will remain at their location at Bernhard-Nocht-Straße. The clinic needed a new provider because the small hospital unit with only 62 beds could not survive economically. The shifting of the patient-admitting unit to the UKE offers the chance to further improve the quality of medical care.

Patient Care on the Wards

The Clinical Department of Bernhard Nocht Institute for Tropical Medicine is remaining a nationwide reference centre for infectious diseases with main emphasis on tropical medicine. In 2005 about 800 patients were admitted to the wards. Besides the treatment of internal diseases in general, expert competence is available in diagnostics and treatment of imported tropical and other infectious diseases (including HIV/AIDS). The Department is specialised in differential diagnosis of infectious diseases (e. g. suspicion for malaria, meningitis, viral haemorrhagic fevers), furthermore HIV-associated diseases, mycobacterial infections and immunological diseases as e. g. immunodeficiency syndromes and autoimmune diseases and specific genetic diseases such as sickle cell anaemia and Familial Mediterranean Fever (FMF). The Clinical Department has been and is still remaining specialised in the treatment of patients with highly contagious diseases. Up to the end of 2005, two isolation units were kept at disposal for these cases – at the new location University Medical Centre Hamburg-Eppendorf a specialised ward is under construction comprising low pressure units to guarantee intensive care of such patients – e. g. with Lassa or Ebola fever.

Outpatient Department for Tropical Medicine and Vaccination Centre

The Outpatient Department is authorized to examine patients in view of specific diseases – mainly infectious diseases imported from tropical and subtropical countries – these patients being referred to us by general practitioners authorized by the Health Insurances. In 2005 about 4700 patients were taken care of in our Outpatient Department, we mainly diagnose cases of unclear fever and unclear diarrhea as well as cases of suspected parasitic diseases. Also skin irritations after stays in tropical areas are frequent indications for differential diagnoses. Further services of the Outpatient Department are consultations after HIV exposition, consultations and vaccinations with regard to rabies as well as consultations following injuries caused by poisonous animals. There are also expatriate precaution checks before and after missions in tropical countries according to occupational health regulations. There is long term patient care in cases of Familial Mediterranean Fever (FMF) and echinococcosis as well as borreliosis. There continues to be several thousands of phone consultations per year to give advice to general practitioners and hospitals in special cases, especially when patients with complicated malaria are treated in intensive care units. As national reference centre for patients with highly contagious diseases, the Department is dealing with questions as far as plausibility checks, diagnostics and patient transport are concerned. This 24 hours service for questions from the field of tropical medicine is going to be maintained in the future. The Vaccination Centre and the Centre for Travel Advice are remaining focal points of the Department's work. About 8000 travel vaccinations were made in 2005.

Centre for Travel Advice

The Centre for Travel Advice (RMZ) was founded in 2001 as a nationwide counselling service working online and by telephone. Information given by the RMZ are evidence-based and adapted to the travellers' personal requirements.

The RMZ offers information for:

- Tourists and business travellers in the entire German-speaking area (by telephone and internet),
- Institutions such as travel agencies (Deutscher Reiseverband) and
- Health insurance companies (e. g. Techniker-Krankenkasse)

Counselling of the RMZ is based on an extensive data compound offering the user complex travelling advice fully automatically within 30 seconds. The system is

used for the operation of our hotline in cooperation with a communication centre run by British Airways. The RMZ is independent from sponsoring by the pharmaceutical industry and did not receive any public funding in the past years. It was granted the award of the German Association of Travel Journalists (VDRJ) for promotion of safe travelling.

www.gesundes-reisen.de

Users:
- 2004: 181,057
- 2005: 214,519

Counselling:
- 2004: 5,707
- 2005: 2,826

Clinical Research

Clinical research of the Department is scheduled to supplement the biomedical research projects of the BNI. Work of the group mainly concentrates on studies regarding the pathophysiology of malaria, there are at present especially investigations as for heart problems and liquid balancing in patients with falciparum malaria. These studies are having effects as regards to the fluid management in patients with severe falciparum malaria. We are furthermore dealing with the significance of Toll like receptors in malaria cases. The Department is maintaining a co-operation with the University Hospital in Peradeniya/Sri Lanka in view of a common study on cardiac and renal failure in patients with severe dengue fever. Further studies are dealing with the elaboration of new schistosomiasis diagnostics.

Continued Education and Teaching

The Clinical Department maintains intensive activities in the scope of continued education and lectures for doctors in training. Together with the BNI a three months' training for students is conducted. In addition, lectures are given for general practitioners and hospital doctors – especially the so-called "Day of Travel Health" (Tag der Reisegesundheit) offered at the beginning of each year with more than 300 participants. There is continued education for house physicians and doctors specialised in tropical medicine working in Hamburg as well as regular lectures for medical students of Hamburg University. The Head of the Clinical Department is authorized to train physicians for three years in internal medicine and for one year in tropical medicine.

Staff members of the Clinical Department are active – often in responsible positions – in Committees of the German Society for Tropical Medicine and International Health (Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit – DTG) for the development of guidelines and travel advice regulations. The DTG worked out a curriculum regarding a "Travel Medicine Certificate" to provide general practitioners with basic knowledge in travel medicine – the Clinical Department was also involved in the elaboration of this curriculum.

In November 2005 the Clinical Department organized a malaria workshop inviting experts from Germany, Austria and Switzerland.

Gerd-Dieter Burchard

Klinische Abteilung

Bericht des Abteilungsleiters

Die Klinische Abteilung des Bernhard-Nocht-Instituts für Tropenmedizin bestand im Jahre 2005 aus den bettenführenden Stationen, der tropenmedizinischen Ambulanz, der Impfambulanz, dem Reisemedizinischen Zentrum sowie der klinischen Forschung. Die Aufgaben der Klinischen Abteilung liegen primär in der Patientenversorgung, zusätzlich in der bundesweiten Beratung von Krankenhäusern und niedergelassenen Ärzten bei schwierigen Differenzialdiagnosen und therapeutischen Fragestellungen, in der reisemedizinischen Beratung, in der Aus-, Fort- und Weiterbildung von Studenten, medizinischem Fachpersonal und Ärzten sowie in der klinischen Forschung. Im Rahmen des Seuchenschutzes ist die Klinik Ansprechpartner bei Verdacht auf Einschleppung hochkontagiöser Erkrankungen. Die Klinische Abteilung wurde zum 1. Januar 2006 in die Trägerschaft des Universitätskrankenhauses Eppendorf (UKE) überführt. Die bettenführende Abteilung wird seitdem als „Sektion Tropenmedizin“ in der Medizinischen Klinik I als eigenständige Abteilung geführt, die tropenmedizinische Ambulanz, die Impfambulanz sowie das Reisemedizinische Zentrum werden weiter am Standort in der Bernhard-Nocht-Strasse bleiben. Anlass für diesen Trägerwechsel war, dass ein kleines Krankenhaus mit 62 Betten heutzutage kaum noch wirtschaftlich geführt werden kann, andererseits bietet die Verlagerung der Betten in das UKE aber auch die Chance, die Qualität der medizinischen Versorgung weiter zu verbessern.

Stationäre Patientenversorgung

Die Klinische Abteilung des BNI bleibt ein überregionales Zentrum für Infektiologie mit Schwerpunkt Tropenmedizin. Im Jahre 2005 wurden in der Abteilung etwa 800 Patienten versorgt. Neben der Behandlung innerer Erkrankungen besteht eine besondere Kompetenz in der Diagnostik und Behandlung von importierten Tropen- und anderen Infektionskrankheiten (einschließlich HIV/AIDS). Die Abteilung ist spezialisiert auf die differenzialdiagnostische Abklärung von Infektionskrankheiten (z. B. Verdacht auf Malaria, Meningitis, virale hämorrhagische Fieber), weiterhin auf die HIV-assoziierten Erkrankungen, auf mykobakterielle Erkrankungen, daneben aber auch auf immunologische Erkrankungen, wie z. B. Immundefektsyndrome und Autoimmunkrankheiten und auf bestimmte genetisch bedingte Erkrankungen, wie z. B. Sichelzellanämie und Familiäres Mittelmeerfieber.

Die Klinik ist und bleibt insbesondere auf die Behandlung von hochkontagiösen Patienten spezialisiert. Für deren Versorgung standen bisher zwei Isolierbettsysteme zur Verfügung, im Bau ist am neuen Standort am UKE eine Station mit Unterdruckzimmern, um auch eine intensivmedizinische Versorgung derartiger Patienten – z. B. mit Lassafieber oder Ebolafieber – zu ermöglichen.

Tropenmedizinische Ambulanz und Impfambulanz

Die Ambulanz ist ermächtigt zur Untersuchung von Patienten zum Nachweis von speziellen Krankheiten – in der Regel von solchen aus tropischen und subtropischen Ländern – auf Überweisung durch Vertragsärzte. Im Jahre 2005 wurden rund 4700 Patienten ambulant betreut. Es werden vorwiegend Abklärungen bei unklarem Fieber, unklaren Durchfällen sowie bei Verdacht auf parasitäre Erkrankungen durchgeführt, auch unklare Hautveränderungen nach Tropenaufenthalt sind eine häufige Differenzialdiagnose. Weitere Serviceleistungen der Ambulanz sind Tropentauglichkeitsuntersuchungen, Beratungen zur HIV-Postexpositionsprophylaxe, Tollwutberatungen und -impfungen, Beratungen und Behandlungen bei Gifttierverletzungen. Es werden auch arbeitsmedizinische Untersuchungen vor und nach Tropenaufenthalt durchgeführt, die sich an den berufsgenossenschaftlichen Grundsätzen orientieren. Speziell werden auch Patienten über längere Zeit betreut mit Familiärem Mittelmeerfieber, mit Echinokokkose sowie auch mit Borrelien-Infektionen.

Die Klinik erhält jährlich mehrere Tausend telefonische Anfragen von niedergelassenen Ärzte und Krankenhäusern zu schwierigen Fällen, insbesondere zur Behandlung schwerer Malariafälle auf Intensivstationen. Als Kompetenzzentrum für Patienten mit hoch ansteckenden Krankheiten werden Fragen zur Plausibilitätskontrolle, zur Diagnostik und zu Verlegungsmodalitäten beantwortet. Dieser 24stündige tropenmedizinische Hintergrunddienst steht nach dem Trägerwechsel weiterhin zur Verfügung.

Die Impfsprechstunde mit reisemedizinischer Beratung ist ein weiterer Schwerpunkt der Arbeit. Hier wurden im Jahr 2005 etwa 8000 reisemedizinische Impfungen durchgeführt.

Reisemedizinisches Zentrum

Das Reisemedizinische Zentrum (RMZ) wurde 2001 gegründet und ist ein überregionaler Beratungsservice, der in erster Linie online und telefonisch arbeitet. Die Informationen des RMZ basieren auf wissenschaftlicher Evidenz und sind den individuellen Bedürfnissen des Reisenden verpflichtet.

Das RMZ erbringt Leistungen für
- Touristen und beruflich Reisende im gesamten deutschsprachigen Raum (Telefon- und Internetservice)
- Institutionen wie Reiseindustrie (Deutscher Reiseverband) und
- Krankenkassen (z. B. Techniker-Krankenkasse)

Grundlage der Arbeitet ist eine umfangreiche Datenbank, mit der innerhalb von 30 Sekunden auch komplexe Reiseberatungen vollautomatisch erstellt werden können. Das System wird in der Zusammenarbeit mit einem Kommunikationszentrum der British Airways zum Betrieb einer reisemedizinischen Hotline eingesetzt. Das RMZ ist unabhängig von Sponsorleistungen durch Pharmafirmen und erhielt in den vergangenen Jahren keine Subventionen aus der Öffentlichen Hand. Für seine Verdienste um den Tourismus wurde das RMZ auf der Internationalen Tourismusbörse in Berlin mit dem Preis des Verbandes der Reisejournalisten (VDRJ) ausgezeichnet.

www.gesundes-reisen.de

Zugriffszahlen:
- 2004: 181.057
- 2005: 214.519

Kostenpflichtige Beratungen:
- 2004: 5.707
- 2005: 2.826

Klinische Forschung

Die Klinische Forschung in der Abteilung unterstützt die biomedizinische Grundlagenforschung im Institut. Der Schwerpunkt der Untersuchungen liegt auf der Pathophysiologie der Malaria, es werden hier insbesondere Untersuchungen zur Herzbeteiligung und zum Flüssigkeitshaushalt bei der Malaria tropica fortgeführt. Diese Untersuchungen haben Auswirkungen auf das Flüssigkeitsmanagement bei Patienten mit schwerer Malaria tropica. Darüber hinaus beschäftigen wir uns mit der Bedeutung von Toll like-Rezeptoren in Entstehung und Verlauf der Malaria tropica.

Eine Kooperation besteht mit der Universitätsklinik in Peradeniya/Sri Lanka, es wurden hier gemeinsame Studien zur Herz- und Nierenbeteiligung bei Patienten mit schwerem Denguefieber durchgeführt. Ein weiterer Schwerpunkt der Forschung liegt in der Entwicklung neuer Diagnostikverfahren für die Schistosomiasis.

Fortbildung und Lehre

In der Fortbildung und Lehre hat die Klinische Abteilung umfangreiche Aktivitäten, es werden in der Klinik Praktikanten, Famuli sowie Studenten im Praktischen Jahr ausgebildet. Die Klinik bietet zusammen mit dem Institut im Rahmen eines Wahlpflichtfaches „Tropen- und Reisemedizin“ einen dreimonatigen Blockkurs für Studenten an. Darüber hinaus finden regelmäßig Veranstaltungen für niedergelassene und Krankenhausärzte statt, zu nennen ist hier insbesondere der jeweils Anfang des Jahres stattfindende „Tag der Reisegesundheit“ mit über 300 Teilnehmern. Mit den niedergelassenen Tropenmedizinern und den niedergelassenen Hausärzten im Einzugsbereich werden regelmäßige Fortbildungsveranstaltungen durchgeführt. Für Studenten des Fachbereichs Medizin der Universität Hamburg wird eine Vorlesung angeboten. Der Leiter der Klinik verfügt über die Weiterbildungsermächtigung für Innere Medizin für drei Jahre und für Tropenmedizin für ein Jahr.

Mitarbeiter der Klinischen Abteilung sind in Ausschüssen der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit (DTG) zur Entwicklung von Leitlinien und für reisemedizinische Beratungen z. T. federführend beteiligt. Die DTG hat für ein Zertifikat „Reisemedizin“ ein Curriculum erarbeitet, um niedergelassenen Ärzten reisemedizinische Grundkenntnisse zu vermitteln, an der Erstellung des Kurs-Curriculums war die Klinische Abteilung beteiligt.

Im November 2005 wurde ein Malaria-Workshop mit Experten aus ganz Deutschland, Österreich und der Schweiz organisiert.

Gerd-Dieter Burchard

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Senior Physician
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Scientific Staff
Dr. Jacob Cramer*
Dr. Stephan Ehrhardt*
Dr. Dominic Wichmann*

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Dr. Stephan Schmiedel*
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Thomas Matz, Medical Controller
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** staff working at BNI on Dec 31st 2005*

Innate immune mechanisms in severe malaria

Clinical Research Group

Zusammenfasssung

Die Mechanismen der angeborenen Immunität sind einerseits essentiell für die Eliminierung parasitärer Infektionserreger wie *Plasmodium falciparum*, andererseits tragen sie zur Pathophysiologie der Malaria bei. Bei Säuglingen und jungen Kindern stellen Zytokine und Immunmediatoren den Hauptmechanismus einer frühen Abwehrstrategie dar. Im Verlauf mehrerer Jahre und wiederholter Infektionen wird in Endemiegebieten allmählich eine so genannte Semiimmunität ausgebildet, wobei dann auch weitere, spezifischere Immunmechanismen erworben werden. Rezeptoren auf der Oberfläche von Makrophagen wie die Toll-like Rezeptoren (TLR) erkennen evolutionär konservierte Strukturen und initiieren die Ausschüttung von Zytokinen. Unsere Untersuchungen befassen sich mit den bei der *P. falciparum* Malaria beteiligten Rezeptoren. Es sollen Polymorphismen innerhalb von Genen aus der TLR-Kaskade detektiert, ihre Frequenz bestimmt und ihr möglicher Einfluss auf die Krankheitsmanifestation der schweren Malaria untersucht werden. Schließlich soll die Interaktion von Ankerproteinen auf der Oberfläche von Plasmodien mit Immunrezeptoren auf Wirtsmakrophagen und ihre immunstimulierende Wirkung analysiert werden.
TLR2, *TLR4* und *TLR9* wurden bereits auf bekannte Polymorphismen hin untersucht. Die Genvariante *TLR4* Asp299Gly wurde assoziiert mit dem Auftreten schwerer Malaria, während Varianten in den *TLR2*- und *TLR9*-Toll/IL-1 Rezeptor Domänen, welche bei Kaukasiern und Asiaten häufig sind, bei Kindern aus Nordghana nicht auftraten. Daher sollen die entsprechenden Gene auf weitere Genvarianten hin untersucht werden und ihre Bedeutung für die Krankheitsmanifestation überprüft werden. Ferner sollen Mäuse, bei denen die Gene einzelner Mitglieder der TLR-Kaskade ausgeschaltet wurden, mit einem murinen Plasmodienstamm infiziert werden, um die Rolle der TLRs für die Zytokinausschüttung sowie die Parasiteneliminierung zu untersuchen.

Introduction

In *Plasmodium falciparum* malaria, host innate immune mechanisms contribute to parasite clearance as well as to disease manifestation. In infants and young children, cytokines and immune mediators confer the first and main immune defense strategy against the parasite before they eventually develop a state of a so called semi-immunity after recurrent infections over the years. Then, additional immune mechanisms are acquired and help to eliminate the parasite more specifically. Pathogen recognition receptors like Toll-like receptors (TLR) have been identified to recognise evolutionary conserved pathogen-associated molecular patterns and initiate the release of cytokines.

Project Description and Results

Our investigation aims at identifying respective receptors involved in *P. falciparum* malaria and to investigate the role of the TLR cascade. Genetic polymorphisms within the TLR cascade are to be identified and evaluated with respect to a potential influence on disease manifestation. Finally, the putative interaction of plasmodial surface anchor proteins with host immune receptors is to be assessed. *TLR2*, *TLR4* and *TLR9* have been screened for known polymorphisms. The *TLR4* Asp299Gly variant has been associated with severe malaria while polymorphisms within the *TLR2*- and *TLR9*-Toll/IL-1 receptor domain common in Caucasians and Asians were completely absent in children from northern Ghana. We, therefore, screen respective genes for additional gene variants and aim at assessing their role in disease manifestation. Furthermore, mice which have been knocked out for members of the TLR cascade are to be infected with murine plasmodial strains to reveal the role of TLRs in initiating cytokine release as well as in controlling parasitaemia.

Selected Publications

- Mockenhaupt FP*, Cramer JP*, Hamann L*, Stegemann MS, Eckert J, Oh NR, Otchwemah RN, Dietz E, Ehrhardt S, Schroder NWJ, Bienzle U, Schumann RR. **2006**. The role of toll-like receptors (TLRs) for malaria pathogenesis: Association of a TLR-4 polymorphism and severe malaria. *Proc Natl Acad Sci U S A*; 103(1): 177-82. Epub 2005 Dec 21 (* contributed equally).
- Cramer JP, Nussler AK, Ehrhardt S, Burkhardt J, Otchwemah RN, Zanger P, Dietz E, Gellert S, Bienzle U, Mockenhaupt FP. **2005**. Age-dependent effect of plasma nitric oxide on parasite density in Ghanaian children with severe malaria. *Trop Med Int Health*; 10(7): 672-80.
- Cramer JP, Mockenhaupt FP, Ehrhardt S, Burkhardt J, Otchwemah RN, Dietz E, Gellert S, Bienzle U. **2004**. *iNOS* promoter variants and severe malaria in Ghanaian children. *Trop Med Int Health*; 9(10): 1074-80.

Cooperating Partners

- Thomas Jacobs, Department of Immunology, BNI
- Rolf D. Horstmann, Department of Molecular Medicine, BNI
- Christoph Hölscher, Research Center Borstel
- Peter H. Seeberger, ETH Zurich, Switzerland
- Ralf R. Schumann, Charité – University Medicine Berlin
- Ansgar W. Lohse, Med. Klinik I, University Medical Centre Hamburg-Eppendorf

Investigators

- Jakob P. Cramer
- Gerd D. Burchard

Evidence for myocardial impairment in African children with falciparum malaria

Clinical Research Group

Zusammenfassung

Daten bei europäischen Reiserückkehrern weisen auf eine myokardiale Funktionseinschränkung bei Patienten mit schwerer Malaria tropica hin. Diese Hypothese sowie deren pathophysiologische Bedeutung sollte bei afrikanischen Kindern validiert und mit metabolischen Parametern korreliert werden. Die Plasmakonzentrationen von N-terminal pro-brain natriuretic peptide (NT-proBNP), Heart-type fatty acid-binding protein (H-FABP), Myoglobin und Creatine kinase muscle-brain (CK-MB) wurden bei 400 afrikanischen Kindern mit schwerer und milder Malaria tropica verglichen. Die Messwerte wurden mit Laktat- und Blutzuckerkonzentrationen, sowie mit dem klinischen Verlauf der Erkrankung korreliert. Wir konnten deutlich erhöhte Konzentrationen kardialer Marker bei Kindern mit schwerer Malaria tropica beobachten. Ursächlich schienen eine Azidose und eine Hypoglykämie zu sein. Beide metabolische Zustände sind nach unseren Daten auf eine Hypovolämie zurückzuführen.

Summary

Recent data from our department suggested that cardiac impairment may play an important role in the pathophysiology of severe *Plasmodium falciparum* malaria. The objective of the present project was to substantiate this finding in a large group of African children and to correlate results with metabolic conditions in these children. Furthermore, the impact of a potential cardiac impairment on outcome of the severe cases was to be assessed. Results may have important implications on the currently ongoing debate on fluid management in severe malaria patients. Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), heart-type fatty acid-binding protein (H-FABP), myoglobin, and creatine kinase muscle-brain (CK-MB) were compared in 400 African children with severe and mild *falciparum* malaria. Plasma levels of these markers were correlated with lactate and glucose blood levels, indicators for hypovolemia, and with clinical outcome. Children suffering from severe malaria and children who died exhibited high to very high levels of cardiac markers, respectively. Lactic acidosis and hypoglycemia resulted in cardiac impairment as defined by elevated levels of circulating cardiac proteins. Our results point to hypovolemia as a major underlying cause for lactic acidosis and hypoglycemia.

Project Description and Results

We analyzed samples from each 200 children suffering from severe and from mild *Plasmodium falciparum* malaria in northern Ghana with respect to biochemical markers of cardiac impairment. We measured plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP). Brain natriuretic peptide (BNP) is a B-type neurohormone synthesized and released from the cardiac ventricles in response to increased wall tension. Serum levels of BNP are increased in patients with heart failure, and these levels increase proportionally to the degree of left ventricular dysfunction. Plasma concentrations of heart-type fatty acid-binding protein (H-FABP) were assessed. FABPs are released rapidly from damaged cells into the circulation and are cleared from the circulation by the kidney with a plasma half-life of 20 minutes. H-FABP is abundant in cardiomyocytes (and brain) and a sensitive and specific biochemical marker for the early assessment of myocardial tissue damage. Myoglobin and creatine kinase muscle-brain (CK-MB) were measured as established markers of myocardial injury. These biochemical indicators were correlated with parasitological and clinical measures to analyse the role of cardiac impairment in severe childhood malaria.

Plasma concentrations of cardiac markers were higher in severe malaria patients as compared to the mild malaria group. Lactic acidosis is a common metabolic condition in children with severe malaria and a powerful predictor of fatal outcome in our study population. The most common cause of acidosis in severely sick children is shock as a result of hypovolemia. In our study, lactate levels correlated with plasma levels of myoglobin, NT-proBNP, H-FABP and, in turn, glucose levels correlated inversely with CK-MB, myoglobin, NT-proBNP and H-FABP. The association of hyperlactatemia with low systolic and diastolic blood pressure and a high heart rate points to hypovolemia as underlying cause. Hypovolemia is a serious problem in our study population and causes deleterious metabolic conditions that lead to cardiac impairment and finally to death. Volume resuscitation in patients with severe malaria is discussed controversially and, though there are hints for beneficial effects of intravenous fluids in severe malaria patients, like in patients with sepsis, carefully executed clinical trials in different age groups are urgently needed. Though cardiac impairment is associated with fatal outcome, in multivariate analysis, lactic acidosis is the leading biochemical parameter predicting death. Extended cardiovascular assessments using echocardiography are now warranted and currently implemented in patients with severe malaria to bring together biochemical and functional measures.

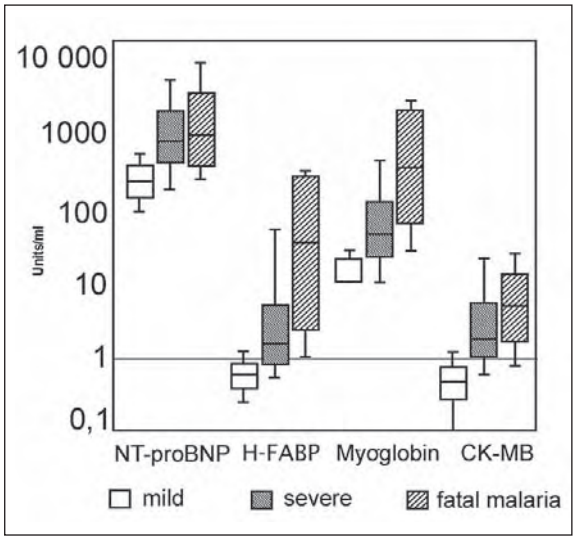

Figure 1: Plasma concentrations of cardiac markers in 400 patients with mild vs. severe malaria vs. patients who died. Presented are log values of medians and percentiles (10%, 25%, 75%, 90%) for NT-proBNP (pg/ml), H-FABP (ng/ml), myoglobin (ng/ml), and CK-MB (ng/ml). The P value for every displayed comparison is < 0.0001 (Kruskal-Wallis-test).

Selected Publications

- Ehrhardt S, Mockenhaupt FP, Anemana SD, Otchwemah RN, Wichmann D, Cramer JP, Bienzle U, Burchard GD, Brattig NW. High levels of circulating cardiac proteins indicate cardiac impairment in African children with severe *Plasmodium falciparum* malaria.
  Microbes Infect. 2005, Aug; 7(11-12):1204-10.
- Ehrhardt S, Wichmann D, Hemmer CJ, Burchard GD, Brattig NW. Circulating concentrations of cardiac proteins in complicated and uncomplicated *Plasmodium falciparum* malaria.
  Trop Med Int Health. 2004, Oct; 9(10): 1099-1103.

Cooperating Partners

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  Department of Molecular Medicine, BNI
- PD Dr. FP Mockenhaupt,
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Investigators

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- Gerd D. Burchard

Diagnosis of Schistosomiasis by PCR

Clinical Research Group

Zusammenfassung

Bei der Diagnose der Schistosomiasis kann es Befundkonstellationen geben die nicht eindeutig zu interpretieren sind. Zu nennen sind hier im Wesentlichen zwei Gruppen. Erstens das Katayamafieber, hier sind Serologie und Einachweis häufig noch negativ. Zweitens Patienten bei denen im Stuhl oder Urin keine Eiernachweis gelingt und wo nachfolgende Biopsien aus Harnblase oder Kolon keine Aussage zum Vitalitätsstatus der gefundenen Eier zulassen; auch die Möglichkeit falsch negativer Biopsiebefunde stellt ein Problem dar.
Zur Lösung dieses Problems haben wir eine pan-Schistosomen real-time PCR mit interner Positivkontrolle etabliert, die humanpathogene Würmer im Blut von Patienten nachweist. In einer ersten Pilotstudie mit 38 serologisch positiven Patienten wurde die Aussagekraft der neuen Methode getestet. Alle Patienten bei denen vitale Schistosomeneier nachgewiesen worden waren, waren PCR-positiv; ebenso alle Patienten mit Katayamafieber. In der Gruppe mit nicht eindeutig zu interpretierenden histologischen Befunden hatten rund 40% eine positive PCR. Die neue Methode scheint sensitiver als die zurzeit gebräuchlichen Verfahren.

Introduction

Diagnostic for schistosomiasis is based on indirect tests like ELISA or IFT as well as on direct detection of schistosoma eggs in stool, urine, bladder or rectal biopsies. In diagnosis of schistosomiasis findings are not always clear. Mainly two situations account for this problem. A) Katayama-fever, a condition where serology and detection of eggs may be negative despite of active disease. B) Patients where no eggs can be detected in stool or urine samples and where no clear statement on the viability of eggs can be given after biopsy from colon or urinary bladder; also false negative biopsy results have to be considered. After treatment with Praziquantel, indirect tests remain positive for many years, maybe even lifelong. Eggs in biopsies will also be detectable for a long time, making it difficult to give a proper statement on viability of these eggs. The purpose of this project was to establish new tools for the detection of schistosomiasis. By this patients can be prevented from unnecessary treatment and cumbering diagnostic procedures like biopsy sampling during coloscopy or cystoscopy.

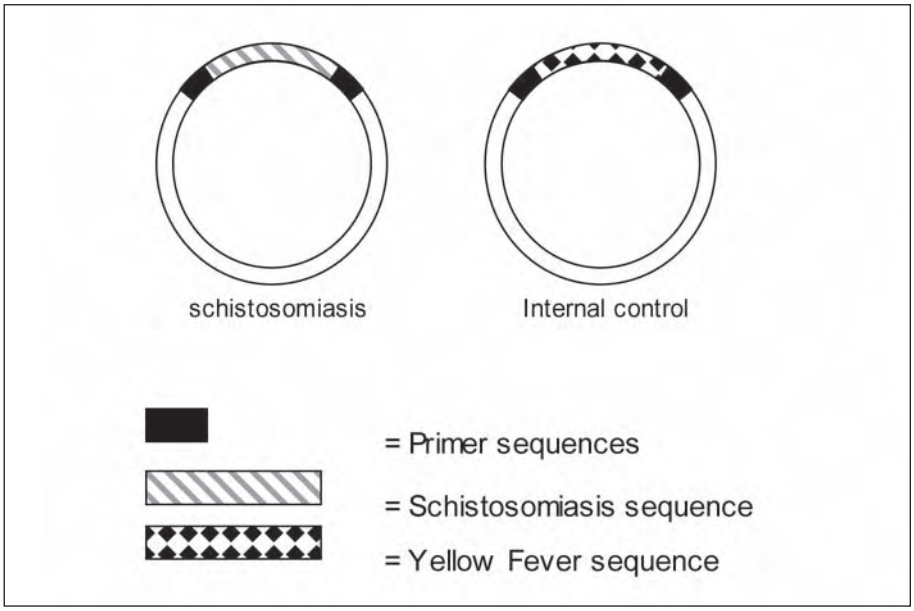

Figure 1

Project Description and Results

Based on published genome sequences we set up a real-time PCR to amplify DNA from adult worms in human plasma.

A plasmid containing a yellow fever virus specific sequence flanked by sequences complementary for primers specific for the schistosomiasis target sequence was created to serve as internal control (Fig.1). This yellow fever virus sequence can be detected by using a separate probe emitting light of a different wave length during the lightcycler® process. By using one pair of primers and two probes the whole diagnostic process can be run in one reaction.

We tested the new diagnostic tool in a small study enclosing 38 patients with positive serology for schistosomiasis (Table 1). All patients with eggs detected in stool or urine samples as well as all patients with Katayama-fever had positive PCR results. In the group of patients with unclear histological findings 40% were PCR positive.

Thus the new real-time PCR is as sensitive as standard methods to detect patients with eggs detected in urine or stool samples. In other conditions (Katayama fever, unclear histological findings, post treatment patients) where standard methods are subjected to restrictions our method seems to be more sensitive.

To evaluate the value for our new PCR as a diagnostic tool for treatment control we have started test series in murine model for schistosomiasis.

Table 1

	Patients (n)	Detection of eggs (n)	+ PCR (%)
Patients with acute disease	11	11	11/11 (100%)
Katayamafever	3	0	3/3 (100%)
Patients with unclear histological findings	24	7	10/24 (42%)
Controls (negative serology)	20	0	0/0 (0%)

Cooperating Partners

- Dr. Christian Drosten,
  Research Group Clinical Virology, BNI
- Prof. Dr. Christoph Grevelding,
  Institute of Parasitology, University of Giessen

Investigators

- Dominic Wichmann
- Gerd D. Burchard
- Christian Drosten
- Christoph Grevelding
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Public Relations
Öffentlichkeitsarbeit

„Mehr Jugend in die Wissenschaft!“ ist der Name des Nachwuchsprogrammes, das das Tropeninstitut 2003/2004 durchführte. Die Bilanz nach 20 Monaten war mehr als positiv: über 1000 Teilnehmerinnen und Teilnehmern kamen zu rund 100 Veranstaltungen. An Praxistagen gab es die Gelegenheit, Laborexperimente durchzuführen, die an den meisten Schulen mangels Ausstattung nicht möglich sind. In den monatlichen „After School Talks“ stellten Wissenschaftler des BNI sich und ihre Arbeit in lockerer Runde vor. Die Einblicke in die Praxis und die Bekanntschaft mit „echten“ Forschern und Labormitarbeitern kam bei den Teilnehmerinnen und Teilnehmern gut an. „Die Einblicke in verschiedene Berufsfelder und Forschungsarbeiten waren äußerst motivierend und haben mich ein erhebliches Stück auf dem Weg ins Berufsleben weitergebracht. Die nette und unkomplizierte Art, mit der uns alle begegnet sind, war für mich ebenfalls eine tolle Erfahrung“, schrieb eine Teilnehmerin. Das Projekt wurde mit 120.000 EUR aus den Mitteln von RIS++ Hamburg unterstützt – einem von der EU-Kommission aufgelegten Programm zur Förderung innovativer Maßnahmen in der Metropolregion Hamburg. Träger des Projekts war die „Vereinigung der Freunde des Tropeninstituts Hamburg e.V.“

Dass der „Blick hinter die Kulissen“ auch für die Großen spannend ist, zeigte der große Erfolg der 1. Hamburger Nacht des Wissens am 29. November 2005. Der Besucherandrang übertraf alle Erwartungen: Rund 2000 Menschen besuchten die Aktionen und Vorträge rund um das Thema Tropenmedizin. Wissenschaftler des Instituts präsentierten im Viertelstundentakt Wissenswertes, Kurioses und Nachdenkliches aus ihren Arbeitsgebieten. Das wehrhafte Immunsystem, Parasitenwahn und leuchtende Würmer fesselten die Zuhörer und führten zu lebhaften Diskussionen. Besonderer Andrang herrschte in der „Welt der Parasiten“, wo die winzigen Erreger von Malaria, Schlafkrankheit und Kala Azar unter dem Mikroskop beobachtet werden konnten und ein gefahrloser Selbsttest zeigte, wie attraktiv man für Stechmücken ist. Dass mit diesem Angebot auch der zukünftige Forschernachwuchs erreicht wurde, zeigt folgender Eintrag der kleine Virginia im Gästebuch: „Ich nehme mir vor, hier später auch mal zu forschen. Bis denn...“. Rund 50 Mitarbeiterinnen und Mitarbeiter des Instituts trugen als Referenten, Ordner und Helfer zum Gelingen des Abends bei. Die Bilanz aller Beteiligten: „Super, hoffentlich gibt es noch eine zweite Nacht des Wissens“.

In der Pressearbeit hatte das Jahr 2005 mit den Auswirkungen der Tsunami-Katastrophe in Südostasien begonnen. Experten des BNI wurden zur Seuchengefahr in den zerstörten Gebieten befragt, und auch bei Reisenden gab es großen Informationsbedarf. Die engagierte Beratung der Tropenmediziner motivierte die in Würzburg ansässige Vogel-Stiftung zu einer äußerst großzügigen Spende. „Die Bekämpfung von Krankheiten, wie sie im Gefolge solcher Katastrophen auftreten setzt eine vertiefte wissenschaftliche Forschung voraus. Es ist uns daher ein Bedürfnis, dem Tropeninstitut in Hamburg eine Spende in Höhe von 30.000 Euro zur Verfügung zu stellen, um genau diesen Forschungszweig zu fördern“, so Dr. Eckernkamp, Verleger und Aufsichtsratsvorsitzender der Vogel Medien Gruppe.

Nacht des Wissens: Sehr beliebt war auch das Schaulabor – selbst die Kleinen stiegen für ein Erinnerungsfoto mutig in den Schutzanzug eines Virologen oder schlüpften mit Mundschutz und Kittel in die Rolle von Ärzten.
A night to remember: future virologists test the atmosphere in the BSL4-protective suit (Night of Science, November 2005).

Forschung am BNI macht Spaß – besonders, wenn das ganze Labor Tropenshirts trägt, wie hier (v.l.n.r.): mit Pipette: Simona John von Freyend, mit Incidin-Liquid: Maja Erdmann, mit *E.coli* XL1 Blue pGEX-MPK9: Anne Scholz, mit Pipet-Boy: Inga Maria Melzer.
Everybody enjoys working at the BNI – the highly motivated PhD teamplayers (Research Group Wiese) presenting the BNI T-Shirt Collection.

Häufigstes Anliegen der Medienvertreter war in 2004 und 2005 die Vogelgrippe, diese sich unaufhaltsam um den Erdball ausbreitende Tierseuche. Das H5N1-Virus, eine drohende Grippe-Pandemie, aber auch das Auftreten anderer Seuchen lösen immer wieder Ängste und Fragen aus, deren Beantwortung alljährlich einen großen Teil der Pressearbeit des BNI ausmacht.

Die „neuen und alten Plagen“ SARS, AIDS und Tuberkulose waren Gegenstand zweier Leibniz-Foren in Hamburg und Brüssel. Wissenschaftler aus vier norddeutschen Leibniz-Instituten stellten aktuelle Themen und Bedürfnisse der Infektionsforschung vor. In Hamburg fand die Podiumsdiskussion vor 270 Bürgern in der Handelskammer statt. Im Brüsseler Hanse-Office Brüssel diskutierten rund 50 geladene Gäste aus dem europapolitischen Umfeld mit den Experten.

Um seltene und schwer aufzuspürende Krankheitserreger, diesmal in Kombination mit Bösewichten und exotischen Ländern, kreist auch die Vorabendserie „M.E.T.R.O.- Einsatz auf Leben und Tod“. In zehn Folgen geht allwöchentlich eine spezialisierte Eingreiftruppe aus Medizinern und Polizisten auf die Jagd nach Parasiten und Banditen. Vorbild für die Geschichten um „Keim & Crime“ waren die in der Tat oft „fabelhaften“ Erlebnisse der Patienten und Ärzte der klinischen Abteilung des Hamburger Tropeninstituts.

Zu einem dauerhaften Renner entwickelt sich die T-Shirt Kollektion „Tropeninstitut Hamburg“. Die drei derzeit erhältlichen Motive sind das Ergebnis eines Kreativwettbewerbs, den Wissenschaftler des BNI initiierten. Seit Oktober 2005 wurden bereits 650 Shirts verkauft. Der Erlös kommt der Vereinigung der Freunde des Tropeninstituts Hamburg e.V. zugute, die sich vor allem die Nachwuchsförderung auf die Fahnen geschrieben hat.

Barbara Ebert

T-Shirt Kollektion „Tropeninstitut Hamburg“

Moskito
blau/brilliant blue

Design:
Claudia & Robert Marggraff

Jungle Junkie
schwarz/black

Design:
Robert Marggraff &
Otto Berninghausen

Weltkarte/Worldmap
grau/grey

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Andreas Krüger

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1. Hamburger Nacht des Wissens – gefördert von der Nordmetall-Stiftung

Wissenschaft im Dialog

Hörsaal, 2. Obergeschoss

Zeit	Titel	Referent
20.30 h	**Bilharziose: Gefahr beim Baden?** Entenbilharziose und Badedermatitis in Deutschland	Privatdozentin Dr. Iris Bruchhaus *Parasitologin*
20.45 h	**Tollwut in Deutschland** Von importierten Viren und Fledermaustollwut	Dr. Christian Drosten *Virologe*
21.15 h	**Es wird heiß: Parasiten unter Hitzeschock** Die Temperatur steuert die Entwicklung von *Leishmania*-Parasiten.	Privatdozent Dr. Joachim Clos *Parasitologe*
21.30 h	**Schlafkrankheit** Schlafkrankheit jenseits der Klischees	Prof. Dr. Christian Meyer *Arzt*
21.45 h	**Malaria: Killer-Parasit N° 1** Der Lebenszyklus von *Plasmodium*	Privatdozent Dr. Volker Heussler *Parasitologe*
22.00 h	**Fünf Minuten Genetik: Schützt Taubheit gegen Infektionen?** Zusammenhänge zwischen Erbkrankheiten und Infektionen	Prof. Dr. Christian Meyer *Arzt*
22.15 h	**Parasiten: Wahn und Wirklichkeit** Seltene Infektionen – oft übersehen	Prof. Dr. Egbert Tannich *Mikrobiologe*
22.30 h	**Wunderbare Biotechnologie: Quallen erleuchten Würmer** Fluoreszierende Eiweiße als Werkzeuge im Labor	Privatdozent Dr. Norbert Brattig *Parasitologe*
22.45 h	**Fünf Minuten Immunologie: Der wehrhafte Körper** Das Immunsystem im Kampf gegen Viren und Parasiten	Dr. Thomas Jacobs *Immunologe*
23.00 h	**Grundlagenforschung: Was sind eigentlich “Omics”?** Genomprojekte und ihr Nutzen	Prof. Dr. Rolf Horstmann *Genetiker*
23.15 h	**Arme Hunde:** Leishmaniose am Mittelmeer	Privatdozent Dr. Joachim Clos *Parasitologe*
Ende: 23.30 Uhr anschließend Mitternachtsvorlesung: „Von SARS bis Vogelgrippe – Daten, Fakten, Hintergründe“		

Wissenschaft im Viertelstundentakt: Voller Saal in der Nacht des Wissens im November 2005.
Different topics every quarter of an hour: Many Hamburg citizens participated in the science dialogue at the BNI in November 2005.

Education and Teaching

Ausbildung und Lehre

Diploma Theses Completed in 2004 and 2005
Diplomarbeiten 2004 – 2005

Parasitology Section / Sektion Parasitologie

Erdmann, Maja	Molekulare Analyse von LmxMPK3, einer Mitogen-aktivierten Proteinkinase aus *Leishmania mexicana*. FACHBEREICH CHEMIE DER UNIVERSITÄT HAMBURG, 11/2004.
Haase, Silvia	Mutagenese-Studien zur Glyoxalase I von *Plasmodium falciparum*. FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 07/2004.
Horstmann, Sebastian	Charakterisierung von rab7 bei *Plasmodium berghei*. FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 01/2004.
Otten, Cécile	Characterization of a new kinesin: *Leishmania major*'s LmaKin1. FAKULTÄT FÜR BIOWISSENSCHAFTEN DER UNIVERSITÄT HEIDELBERG, 06/2004.
Tolstrup, Jörn	Proteomanalyse Cysteinproteinase-überexprimierender *Entamoeba histolytica*. FACHBEREICH BIOLOGIE DER UNIVERSITÄT WÜRZBURG, 07/2004.
Baron, Jens	Klonierung und Charakterisierung der Cysteinprotease Calpain-7 des Malariaparasiten *Plasmodium berghei*. FACHBEREICH BIOLOGIE DER UNIVERSITÄT DARMSTADT, 02/2005.
Engel, Stefanie	Klonierung und rekombinante Expression von mitotischen Kinesinen aus *Plasmodium falciparum*. HOCHSCHULE ANHALT (FH), KÖTHEN, 06/2005.
Krieger, Jana	Entwicklung diagnostischer real-time PCR Assays zum Nachweis der Darmprotozoen *Entamoeba histolytica, Entamoeba dispar, Giardia lamblia und Cryptosporidium parvum* aus humanen Stuhlproben. FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 06/2005.
Mettler, Ramona	Optimierung der 2-dimensionalen Gelelektrophorese für Proteinextrakte aus *Leishmania* spp. und Differenzierungsanalyse von *Leishmania donovani* nach Geldanamycin-Behandlung. HOCHSCHULE ANHALT (FH), KÖTHEN.
Puls, Gesa	Molekulare Untersuchungen von Mitogen-aktivierten Proteinkinasen aus *Leishmania mexicana*. FAKULTÄT III DER TECHNISCHE UNIVERSITÄT BERLIN, 09/2005.
Sturm, Angelika	Identifizierung von *Plasmodium* Proteasen, die an der Freisetzung der Merozoiten aus infizierten Leberzellen beteiligt sind. FACHBEREICH BIOLOGIE DER UNIVERSITÄT DARMSTADT, 01/2005.
Treeck, Moritz	Untersuchungen zum zielgerichteten Proteintransport in *Plasmodium falciparum* (Welch, 1897). FACHBEREICH BIOCHEMIE DER UNIVERSITÄT HAMBURG, 10/2005.
Wörth, Anke	Analysen der Proteasen PFC0495w, PFB0340c und PF0230c des Malariaerregers *Plasmodium falciparum*. FACHBEREICH BIOTECHNOLOGIE DER FACHHOCHSCHULE MANNHEIM, 04/2005.

Medical Microbiology Section / Sektion Medizinische Mikrobiologie

Berkau, Anne-Jo	Untersuchungen zur zellspezifischen Regulation von Granulysin. FACHBEREICH BIOLOGIE DER UNIVERSITÄT KIEL, 06/2004.
Maczurek, Annette	Funktionelle Untersuchungen des Nichtstrukturproteins 4B des Gelbfiebervirus mittels „charged-to-alanine scanning“ Mutagenese und Protein-Interaktionsstudien. LEHRSTUHL FÜR TECHNISCHE MIKROBIOLOGIE DER TECHNISCHEN UNIVERSITÄT MÜNCHEN, 04/2004.
Erdmann, Hanna	Untersuchung zur Regulation von T-Zellen durch Interaktion des negativen Costimulators PD-1 mit seinen Liganden PD-L1 und PD-L2. STUDIENGANG BIOCHEMIE/MOLEKULARBIOLOGIE DER UNIVERSITÄT HAMBURG, 08/2005.
Gräwe, Stefanie	The role of CD38 in the experimental model of Leishmaniasis. FACHBEREICH BIOCHEMIE DER UNIVERSITÄT HAMBURG, 12/2005.
Höchst, Bastian	Einfluss von HCV-NS3-Fragmenten auf die enzymatische Aktivität der Proteinkinase C. STUDIENGANG BIOLOGIE DER RHEINISCHEN FRIEDRICH-WILHELMS-UNIVERSITÄT BONN, 09/2005.
Kamdem Medom, Berthe	Untersuchung der *in vitro* Inhibition verschiedener Proteinkinase C-Isoformen durch die Domäne 2 des Nicht-Strukturprotein 3 (NS3) des Hepatitis C-Virus. STUDIENGANG BIOTECHNOLOGIE DER HOCHSCHULE FÜR ANGEWANDTE WISSENSCHAFTEN HAMBURG, 06/2005.
Lucke, Judith	Generierung von zwei Zelllinien mit stabiler HCV-NS3-Helikase Expression und erste Charakterisierung hinsichtlich Störung von Proteinkinase C-Aktivität. STUDIENGANG BIOTECHNOLOGIE DER HOCHSCHULE FÜR ANGEWANDTE WISSENSCHAFTEN HAMBURG, 2005.
Polansky, Julia	Physiology of $CD4^+CD25^+$ regulatory T cells: role of T cell receptor-mediated phosphorylation and PoxP3. STUDIENGANG BIOCHEMIE/MOLEKULARBIOLOGIE DER UNIVERSITÄT HAMBURG, 05/2005.
Schommer, Nina	Charakterisierung infizierter dendritischer Zellen im experimentellen Modell der Leishmaniose. FACHBEREICH BIOLOGIE DER TECHNISCHE UNIVERSITÄT DARMSTADT, 12/2005.
Schreiber, Sandra	Charakterisierung einer HIV-1-Viruspopulation mit Aminosäureaustauschen und unterschiedlicher N-Glykolysierung im gp120 V3 loop. FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 07/2005.
Warlich, Michael	Untersuchung von Gelbfiebervirus NS4B „charged-to-alanine scanning“ Mutanten. FAKULTÄT FÜR BIOLOGIE DER UNIVERSITÄT BIELEFELD, 12/2005.

Tropical Medicine Section / Sektion Tropenmedizin

Afrane, Yaw Asare	Influence of urban and peri-urban agriculture on the transmission of malaria in Kumasi, Ashanti region. DEPARTMENT OF BIOLOGY, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, GHANA.
Debrah, Alexander Yaw	Analysis of microfilarial loads in the skin of onchocerciasis patients after treatment with doxycycline and ivermectin. DEPARTMENT OF BIOLOGY, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, GHANA.
Kutin, Kwesi	Transmission of Onchocerciasis by *Simulium sanctipauli* “Pra” form in the upper Denkyira District, Ghana after mass ivermectin treatment. DEPARTMENT OF BIOLOGY, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, GHANA.

Theses Completed in 2004 and 2005
Dissertationen 2004 – 2005

Parasitology Section / Sektion Parasitologie

Isermann, Kerstin — Die Peroxiredoxine des Nematoden *Caenorhabditis elegans*.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 05/2004.

Khawaja, Fareed Ehjaz — Entwicklung einer Amöbiasisvakzine: Charakterisierung eines Epitops des 170 kDa Oberflächenlektins von *Entamoeba histolytica*.
FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 01/2004.

Kuhn, Daniela — *In vitro* und *in vivo* Analyse von LmxPK4, einer MAP Kinase Kinase aus *Leishmania mexicana*.
FACHBEREICH CHEMIE DER UNIVERSITÄT HAMBURG, 09/2004.

Wanders, Petra — *In vitro* und *in vivo* Charakterisierung einer LmxMPK5-Deletionsmutante in *Leishmania mexicana*.
TIERÄRZTLICHE HOCHSCHULE HANNOVER, 02/2004.

Das Gupta, Robin — Polyamine in *Plasmodium falciparum*: Einfluss von Inhibitoren der Syntheseenzyme auf Polyamingehalt und Wachstum.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 12/2005.

Haider, Nashya — The characterization of the spermidine synthase from *Plasmodium falciparum* and *Caenorhabditis elegans*.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 11/2005.

Harder, Simone — Charakterisierung von zwei stadien-spezifischen Proteinen des parasitischen Protozoons *Leishmania donovani* (Ross, 1903).
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 05/2005.

Müller, Ingrid B. — Funktionelle Analyse des Polyaminstoffwechsels in *Plasmodium falciparum*.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 11/2005.

Nowak, Nicolas — Einfluss der Cysteinpeptidasen auf die Pathogenität von *Entamoeba histolytica* (Schaudinn, 1903).
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 03/2005.

Reiling, Linda — Varianten der *Leishmania major* (Yakimov & Schokov, 1915) ΔclpB-Mutante: Virulenz und Immunantwort im Mausmodell.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 02/2005.

van de Sand, Claudia — Überlebensstrategien von *Plasmodium berghei* (Vincke & Lips, 1948) in Hepatozyten.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 11/05.

Medical Microbiology Section / Sektion Medizinische Mikrobiologie

Lieke, Thorsten — Beteiligung von murinen Natürlichen (NK)-Zellen an der Immunantwort gegen intrazelluläre und extrazelluläre *Trypanosoma cruzi*.
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 11/2004.

Voßmann, Markus — Neutralisation von Varianten des Humanen Immundefizienz Virus Typ I (HIV-1), West-Nil Virus und Hantaan Virus mit modifiziertem humanen Serumalbumin (Hsa).
FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 12/2004.

Kirst, Martin	Herstellung und Charakterisierung eines anti-HIV-Inhibitors basierend auf modifiziertem Serum Albumin. FACHBEREICH PHARMAKOLOGIE DER UNIVERSITÄT HEIDELBERG, 07/2005.
Osterloh, Anke	Hitzeschockprotein 60 (Hsp60) als immunologischer Signalverstärker in der Maus (*Mus musculus*). FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 08/2005.
Specht, Sabine	Antagonism between IL-4 and IL-10 in colitis and a helminth infection in *Mus musculus*. FACHBEREICH BIOLOGIE DER UNIVERSITÄT HAMBURG, 03/2005.
Vieth, Simon	Sequenzanalyse der L-RNA von Lassavirus und Aufbau moderner Nachweissysteme für hochpathogene Arenaviren. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 02/2005.

Tropical Medicine Section / Sektion Tropenmedizin

Adusei, Afua	Symptomatische Bakteriämie als Differentialdiagnose der schweren Malaria im Säuglings- und Kleinkindesalter. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 02/2004.
Niesporek, Silvia	Assoziationen von TAP1/LMP2-Promotor-Varianten und Allelen des TAP1- und LMP2-Gens mit den Manifestationsformen der *Plasmodium-falciparum*-Infektion. CHARITÉ – UNIVERSITÄTSMEDIZIN BERLIN 11/2004.
Schmidt, Martin	Untersuchung zum Vorkommen GJB2-assoziierter Gehörlosigkeit in Kenia, Ostafrika. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 06/2004.
Höckh, Florestan Gerald	Untersuchungen zur biologischen Wirkung von *Onchocerca volvulus*-Proteinen auf Monozyten/Makrophagen in vitro. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 07/2005.
Marks, Florian	Untersuchungen zur Resistenz von *Plasmodium falciparum* gegen Sulfadoxin/Pyrimethamin bei intermittierender Malariatherapie. FACHBEREICH CHEMIE (PHARMAKOLOGIE) DER UNIVERSITÄT HAMBURG, 11/2005.
Schwohl, Aline	Expression von Prostaglandin E_2 in Entwicklungsstadien der Filarie *Onchocerca* sowie in Wirtszellen von Onchozerkosepatienten. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 04/2005.

Clinical Department / Klinik

Kobbe, Robin	Epidemiologische, klinische und pathophysiologische Aspekte von 800 stationär behandelten Fällen von importierter Malaria bei Erwachsenen der Jahre 1996 bis 2001. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 04/2005.

Habilitations 2004 and 2005
Habilitationen 2004 – 2005

Fischer, Peter	Untersuchungen zur Bekämpfung humanpathogener Filarieninfektionen. FACHBEREICH MEDIZIN DER UNIVERSITÄT HAMBURG, 03/2004.

Courses on Tropical Medicine 2004 and 2005

The objective of the annual course is to prepare physicians for professional tasks in tropical and subtropical countries and to enable them to preventively care for visitors of warm climates, to diagnose and to treat imported tropical diseases and perform the relevant consultations. Teaching concentrates on the pathogenesis, diagnosis, clinical entities, treatment, epidemiology, and prophylaxis of parasitic, bacterial, viral and non-transmissible diseases of tropical countries. Addressed are the biology, epidemiology, and control of the causative agents, vectors and reservoirs. Additional topics include the characteristics of the various clinical disciplines in the tropical environment, problems of private and public health care in poor countries as well as structures and performance of developmental cooperation and disaster missions in medicine.

The central topics of the course are human diseases characteristic for tropical climates. The curriculum is divided into twelve sections of one week each. Clinical differential diagnosis is the major guideline for the curriculum because most of the participants are practising physicians. Taxonomy is the second criterion in order to facilitate systematic learning. Entomology is considered in its relation to the etiology and transmission of disease and therefore follows clinical classifications. Malaria, because of its outstanding relevance, is regarded a separate topic.

The following curriculum is accepted by the German Federal Board of Physicians to be part of the official training programme for physicians to specialize in tropical medicine, and also by the American Society of Tropical Medicine and Hygiene. The course starts out with one week of introductions reaching from the techniques of microscopy to fundamental immunology. In week 2, basic epidemiology and malaria and in weeks 3 and 4, systemic febrile infections are dealt with. The diseases are put in order according to relevance, clinical similarities and taxonomic aspects. They are followed by intestinal diseases in week 5, and in weeks 6 and 7 by helminth infections, which often share the hallmark

Course on Tropical Medicine 2004 Photographer: Klaus Jürries

of eosinophilia and primarily affect the intestine or the skin. Tropical dermatology including cutaneous leishmaniasis and leprosy are presented in week 8. The main topic of week 9 is HIV/AIDS, addressing in detail the management of tuberculosis and opportunistic infections in tropical countries. Week 10 is dedicated to travel medicine, simple laboratory techniques and tropical peculiarities of the established medical disciplines, e.g. in neurology, surgery, and gynaecology, and in weeks 10 and 11 specific problems in public health and developmental cooperation are being discussed. Week 12 contains summaries of clinical entities and exercises, including paedicatrics, haematology and vaccination programmes, and in week 13 differential diagnosis, repetitions as well as practical and theoretical examinations are scheduled.

Teaching is offered daily from 9 a.m. to 4:15 p.m. A total of more than 300 lessons are given, accompanied by 40 hours of practical, mostly microscopic exercises. In addition, the German reference library for literature on tropical medicine, and full internet access are available for private studies. In 2005, 520 credit points were awarded by the Hamburg Board of Physicians.

The courses of the years 2004 and 2005 were held from April to June. In 2004, 40 physicians and biologists participated, and 39 of them received diplomas. In 2005, diplomas were awarded to 53 of the 54 participants.

Week 1:	Introductions and essentials, incl. immunology, health sciences, exercises
Week 2:	Systemic infections 1: Malaria incl. entomology, laboratory methods, exercises, principles in epidemiology
Week 3:	Systemic infections 2: Viral and bacterial infections incl. entomology, laboratory methods, exercises
Week 4:	Systemic infections 3: Other protozoal and viral diseases, entomology, laboratory methods, exercises
Week 5:	Intestinal diseases by protozoa, bacteria and viruses incl. laboratory methods, exercises
Week 6:	Helminth infections incl. entomology, systemic mycoses, laboratory methods, exercises
Week 7:	Helminth infections incl. exercises
Week 8:	Skin and veneral diseases, mycobacteriology, ophthalmology
Week 9:	HIV infection/AIDS, tuberculosis
Week 10:	Neurology, surgery, gynaecology, travel medicine, Public Health, planning, financing, and implementation of health projects, essential drugs
Week 11:	Specific problems in certain disciplines incl. psychiatry, environmental medicine, differential diagnosis, venomous animals
Week 12:	Specific problems in certain disciplines incl. paediatrics, malnutrition, haematology and malignancies in the tropics, mother-child-care, vaccination programmes, reproductive health
Week 13:	Differential diagnosis, repetitions, final examination

Kursus für Tropenmedizin 2004 und 2005

Ziel des Kurses ist es, entsprechend der Weiterbildungsordnung der deutschen Ärztekammern Ärzte auf eine berufliche Tätigkeit in den Tropen und Subtropen vorzubereiten und sie in die Lage zu versetzen, Besucher der Tropen und Subtropen präventivmedizinisch zu betreuen, importierte Tropenkrankheiten zu erkennen und zu behandeln und entsprechende Beratungen durchzuführen.

Das zentrale Thema des Kurses ist die Darstellung der tropentypischen Krankheiten des Menschen. Im Vordergrund der Lehrinhalte stehen dabei die Pathogenese, Diagnose, Klinik, Therapie, Epidemiologie und Prophylaxe der parasitären, bakteriellen, viralen und nicht-übertragbaren Tropenkrankheiten. Auch die Biologie, Epidemiologie und Bekämpfung der entsprechenden Erreger, Überträger und Reservoire werden berücksichtigt. Weitere Inhalte sind Besonderheiten der einzelnen klinischen Fachgebiete in den Tropen, Probleme der privaten und öffentlichen Gesundheitsversorgung in armen Ländern sowie Organisation und Verfahren der medizinischen Entwicklungszusammenarbeit und Katastrophenhilfe.

Der Lehrplan ist in zwölf thematisch gegliederte Abschnitte von einwöchiger Dauer unterteilt. Oberstes Gliederungsprinzip ist die klinische Differentialdiagnose, da klinisch tätige Ärzte den größten Anteil der Teilnehmer des Kursus stellen. An zweiter Stelle ist die Taxonomie berücksichtigt, um das systematische Lernen zu erleichtern. Die Entomologie ist unter medizinischen Aspekten im wesentlichen eine Lehre von der Krankheitsübertragung und ist klinischen Gliederungsprinzipien untergeordnet. Die Malaria wird wegen ihrer herausragenden Bedeutung gesondert berücksichtigt.

Kursus für Tropenmedizin 2005 Fotograf: Klaus Jürries

Mit folgender Gliederung wird der Kursus von der Bundesärztekammer als Teil der Weiterbildung zur Zusatzbezeichnung „Tropenmedizin“ und von der American Society of Tropical Medicine and Hygiene (ASTMH) anerkannt:

Woche 1:	Einführungen und Grundlagen einschl. Immunologie, Gesundheitswissenschaften, Übungen
Woche 2:	Generalisierte Infektionen 1: Malaria einschl. Entomologie, allgemeine Epidemiologie, Labordiagnostik, Übungen
Woche 3:	Generalisierte Infektionen 2: Virale und bakterielle Infektionen einschl. Entomologie, Labordiagnostik, Übungen
Woche 4:	Generalisierte Infektionen 3: Andere Protozoen- und Virusinfektionen einschl. Entomologie, Labordiagnostik, Übungen
Woche 5:	Darmerkrankungen durch Protozoen, Bakterien und Viren einschl. Labordiagnostik, Übungen
Woche 6:	Wurmerkrankungen einschl. Entomologie, Systemmykosen, Übungen
Woche 7:	Wurmerkrankungen einschl. Entomologie, Übungen
Woche 8:	Hauterkrankungen, venerische Erkrankungen, mykobakterielle Erkrankungen, Ophthalmologie
Woche 9:	HIV Infektionen, AIDS, Tbc
Woche 10:	Neurologie, Chirurgie, Gynäkologie, Reisemedizin, öffentliches Gesundheitswesen, Planung, Finanzierung, Durchführung von Gesundheitsprojekten, wesentliche Medikamente
Woche 11:	Spezielle Probleme einzelner Fachgebiete, insbesondere Psychiatrie, Umweltmedizin, Gifttiere, Differentialdiagnose
Woche 12:	Spezielle Probleme einzelner Fachgebiete, insbesondere Pädiatrie, Fehl- und Mangelernährung, Mutter-Kind-Vorsorge, Impfprogramme, reproduktive Gesundheit
Woche 13:	Differentialdiagnose, Repetitionen, Abschlussprüfung

Der Kursus beginnt mit einer Woche der Einführungen, die von der Technik des Mikroskopierens über immunologische Grundlagen bis zur allgemeinen Epidemiologie reichen. In den Wochen 2 bis 4 werden fieberhafte Allgemeinerkrankungen dargestellt, die untereinander nach Bedeutung, differentialdiagnostischer Ähnlichkeit und nach taxonomischen Gesichtspunkten geordnet sind. In Woche 5 folgen Darmkrankheiten, in Woche 8 Hauterkrankungen und dazwischen in Woche 6 und 7 Wurminfektionen, die überwiegend Darm oder Haut betreffen und häufig das gemeinsame differentialdiagnostische Charakteristikum einer Eosinophilie aufweisen. Die 9. Woche ist HIV-Infektionen und AIDS und Woche 10 speziellen Fragen der medizinischen Entwicklungszusammenarbeit und des öffentlichen Gesundheitswesens gewidmet. In Woche 11 werden tropentypische Besonderheiten der etablierten klinischen Fachgebiete, wie der Neurologie und der Gynäkologie, behandelt, und in Woche 12 Pädiatrie, Mutter-Kind-Vorsorge, Impfprogramme sowie reproduktive Gesundheit. Woche 13 enthält differentialdiagnostische Zusammenfassungen und Repetitionen sowie die theoretischen und praktischen Prüfungen und schliesslich die Abschlussfeier.

Lehrveranstaltungen werden täglich von 9 Uhr bis 16.15 Uhr angeboten. Insgesamt werden mehr als 300 Stunden Vorlesungen gehalten und 40 Stunden praktischer, überwiegend mikroskopischer Übungen ausgerichtet. Zum Selbststudium steht die deutsche Referenzbibliothek für tropenmedizinische Literatur zur Verfügung. 2005 wurden für die Kursteilnahme 520 Fortbildungspunkte durch die Ärztekammer Hamburg vergeben.

Die Kurse der Jahre 2004 und 2005 fanden jeweils von April bis Juni statt. 2004 nahmen 40 Ärzte und Biologen an dem Kursus teil; 39 Teilnehmer erhielten das Diplom. 2005 erwarben 53 der 54 Teilnehmer das Diplom.

Faculty Course on Tropical Medicine
Dozenten des Kurses für Tropenmedizin

Institute faculty
Hausdozenten

Dr. Gisela Bretzel
Prof. Dr. Gerd D. Burchard
Prof. Dr. Dietrich W. Büttner
Dr. Christian Drosten
Dr. Frank Ebert
Dr. Stefan Ehrhardt
Dr. Jennifer Evans
Dr. Peter Fischer
Prof. Dr. Bernhard Fleischer
Prof. Dr. Rolf Garms
Dr. Sebastian Graefe
PD Dr. Stephan Günther
Prof. Dr. Rolf Horstmann
Dr. Helmut Jäger
Dr. Stefanie Kramme
Dr. Andreas Krüger
Dr. Ute Lippert
Dr. Florian Marks
Dr. Jens Matten
PD Dr. Jürgen May
Prof. Dr. Christian G. Meyer
Prof. Dr. Paul Racz
Dr. Jan Rybniker
Dr. Stefan Schmiedel
Prof. Dr. Herbert Schmitz
Prof. Dr. Justus Schottelius
Dr. Hinrich Sudeck
Prof. Dr. Egbert Tannich
Dr. Klara Tenner-Racz
Dr. Christian Timmann
Prof. Dr. Rolf D. Walter

Guest faculty
Auswärtige Dozenten

- Prof. Xaver Baur, Hamburg Port Health Center, Zentrum für Hafen-/Flughafenärztliche Dienste und Schifffahrtsmedizin
- Dr. Assia Brandrup-Lukanow, Gesellschaft für Technische Zusammenarbeit (GTZ), Eschborn
- Dr. Matthias Brockstedt, Berlin
- Dr. Christoph Dehnert, Medizinische Klinik und Poliklinik, Universität Heidelberg
- Dr. Alois Dörlemann, Health-Focus GmbH, Potsdam
- Dr. Karl-Peter Faesecke, Hyperbaric Training Center, Hamburg
- Dr. Thomas Fenner, Hamburg
- Herr Aandreas Fertig, Ärzte ohne Grenzen, Bonn
- Dr. Marcellus Fischer, Bundeswehrkrankenhaus Hamburg
- Frau Hanne Fleischmann, Missionsärztliches Institut, Würzburg
- Dr. Gertrud Helling-Giese, Ärztlicher Dienst des Deutschen Entwicklungsdienstes (DED), Bonn
- Dr. Klaus Hoffmann, Zentrum für Psychiatrie, Landeskrankenhaus, Reichenau
- Prof. Dr. Volker Klauß, Augenklinik der Universität München
- Dr. jur. Bernd Koch, Berufsgenossenschaft der Chemischen Industrie, Köln
- Dr. Wolfgang Krahl, Bezirkskrankenhaus Haar, Haar
- Prof. Dr. Michael Krawinkel, Institut für Ernährungswissenschaft, Gießen
- Dr. Philipp Langenscheidt, Hufeland-Klinik, Weimar
- Prof. Dr. Michael Leichsenring, Universitäts-Kinderklinik Ulm
- Prof. Dr. Dieter Mebs, Institut für Rechtsmedizin, Frankfurt
- Frau Silvia Miksch, Missionsärztliches Institut, Würzburg
- Dr. Matthias von Mülmann, Medizinischer Dienst der Lufthansa AG, Frankfurt (M)
- PD Dr. Stefan Peters, Universitätsklinikum Schleswig-Holstein, Campus Lübeck
- Frau Dr. Sabine Rüsch-Gerdes, Forschungszentrum Borstel

- Prof. Dr. Genevieve Scarisbrick, Obernzell
- Dr. Johannes Schäfer, Tropenklinik, Paul-Lechler-Krankenhaus, Tübingen
- Prof. Dr. Erich Schmutzhard, Universitätsklinik für Neurologie, Innsbruck
- PD Dr. Walter Sigge, Universitätsklinikum Schleswig-Holstein, Campus Lübeck
- PD Dr. August Stich, Missionsärztliche Klinik, Würzburg
- Herr Tankred Stöbe, Ärzte ohne Grenzen, Bonn
- Dr. Jan van Lunzen, Universitätsklinikum Hamburg-Eppendorf
- Dr. Gunther von Laer, Auswärtiges Amt/ Gesundheitsdienst, Berlin
- Dr. med. Klaus J. Volkmer, Centrum für Reisemedizin, Düsseldorf
- Prof. Dr. Sawko Wassilew, Klinik für Dermatologie, Krefeld

Lectures and Seminars of the BNI at the University of Hamburg
Lehrveranstaltungen des BNI an der Universität Hamburg

Fachbereich Medizin	Winter-semester	Sommer-semester	Nr im Vorle-sungsverz.
Einführung in die Tropenmedizin/ Grundlagen der Tropenmedizin Vorlesung, 1 st. *Rolf Horstmann, Christian Timmann, Jürgen May*	X	X	04.611
Grundlagen der Infektionsepidemiologie 1 st. *Jürgen May, Christian Meyer, Christian Timmann*	X	X	04.612
Seminar über aktuelle Probleme in der Virologie 1 st. *Herbert Schmitz und MitarbeiterInnen*	X	X	04.613
Einführung in die Epidemiologie der Tropenkrankheiten gztg. n.V. *Rolf Horstmann, Christian Meyer, Jürgen May*	X	X	04.615
Klinik der Tropenmedizin mit Patientenvorstellung 1 st. *Gerd Burchard, Hinrich Sudeck, Christian Meyer*	X	X	04.616
Immunologische Aspekte der Erreger-Wirtsbeziehungen bei Infektionskrankheiten 2 st. n.V. *Paul Racz, Klara Tenner-Racz*	X	X	04.617
Ringvorlesung: Viren und Diagnostik Tropische Viren: Klinik, Diagnostik, Pathogenese und Molekularbiologie 2 st. *Herbert Schmitz, Peter Borowski, Stephan Günther, Christian Drosten, Michael Schreiber*	X	X	04.618
Einführung in die molekulare Parasitologie 2 st. *Egbert Tannich und MitarbeiterInnen*	X	X	04.619
Biologie und Diagnostik tropischer Infektionserreger 2 st. *Egbert Tannich und MitarbeiterInnen*	X	X	04.620
Aktuelle Ergebnisse der parasitologischen Grundlagenforschung, Seminar; 2 st. *Egbert Tannich und MitarbeiterInnen*	X	X	04.621
Klinik der Tropenkrankheiten Vorlesung, 1 st. *Gerd-Dieter Burchard, Christian Meyer, Hinrich Sudeck*	X	---	04.622
Zelluläre und Molekulare Immunologie 2 st. *Bernhard Fleischer und MitarbeiterInnen*	X	X	04.827
Immunologie für Mediziner Vorlesung, 1 st. *Bernhard Fleischer, Friedrich Haag, Thorsten Krieger, Friedrich Nolte*	X	X	41.030
Immunologisches Literaturseminar 1 st. *Bernhard Fleischer und MitarbeiterInnen*	X	X	04.828
Seminar über aktuelle Probleme der Immunologie 1 st. *Bernhard Fleischer und MitarbeiterInnen*	X	X	04.829
Immunologisches Praktikum 14 tg., n.V. *Bernhard Fleischer und MitarbeiterInnen*	X	X	04.831
Mechanismen der Signaltransduktion und Regulation der Genexpression in Eukaryoten (Seminar) 2 st. *Martin Wiese, Volker Heussler*	X	X	04.826

Fachbereich Biologie	Winter-semester	Sommer-semester	Nr im Vorle-sungsverz.
Molekulare Parasitologie (Seminar) 2 st. *Rolf D. Walter, Eva Liebau*	---	X	14.437
Einführung in die Protozoologie (unter Berücksichtigung frei lebender und parasitischer Protozoen sowie Einzeller als Krankheitserregern bei Mensch und Tier mit praktischen Übungen) Vorlesung, 2 st. *Justus Schottelius*	---	X	14.425
Spezielle Protozoologie: Protozoen als Parasiten und Krankheitserreger bei Mensch und Tier mit aktuellem Stand der protozoologischen Forschung (mit mikroskopischen Übungen) 2 st. *Justus Schottelius*	X	---	14.428
Molekulargenetisches Praktikum: Von der DNA zur Enzymaktivität 10 tg. n.V. *Iris Bruchhaus, Volker Heussler*	X	X	14.128
Anleitung zu wissenschaftlichen Arbeiten tägl. ganztägig n.V. *Rolf D. Walter u.a.*	---	X	14.480

Fachbereich Chemie	Winter-semester	Sommer-semester	Nr im Vorle-sungsverz.
Biochemische Analytik für Studenten der Biochemie, Biologie und Chemie Vorlesung, 2 st. *Joachim Clos und andere Dozenten der Biochemie*	---	X	00.471
Molekularbiologie I für Studenten der Biochemie, Biologie und Chemie Vorlesung, 1 st. *Joachim Clos, Thomas Kruppa*	X	---	00.474

Wahlfach Tropen- und Reisemedizin

für Studierende der Medizin der Universität Hamburg
10. Januar – 25. März 2005

Tutoren

Prof. Dr. Gerd-Dieter Burchard *(Tutor für klinische Tropenmedizin)*
Prof. Dr. Egbert Tannich *(Tutor für theoretische Tropenmedizin)*

Seminar Theoretische Tropenmedizin

E. Tannich	Mikro- und Makroparasiten
A. Krüger	Insekten als Krankheitsüberträger
R. Horstmann	Mechanismen der Organschädigung bei der Malaria
R. Horstmann	Angeborener und erworbener Schutz vor Malaria
B. Fleischer	Besonderheiten der Wurminfektionen
S. Günther	Lassa, Ebola und andere Tropenviren
E. Tannich	Direkter und indirekter Parasitennachweis
R. Walter	Medikamentenresistenz
B. Fleischer	Probleme der Impfstoffentwicklung
M. Vogel	Umgang mit Patienten aus anderen Kulturkreisen
B. Ebert	Berufsbilder in der Tropenmedizin

Seminar Problemorientierte klinische Tropenmedizin

G. D. Burchard	Tropenmedizin zwischen Infektionskrankheiten und Öffentlichem Gesundheitswesen
G. D. Burchard	Differenzialdiagnose Fieber
S. Ehrhardt	Differenzialdiagnose der Splenomegalie
U. Lippert	Differenzialdiagnose der Hepatopathie
M. Fischer	Differenzialdiagnose von Exanthemen nach Tropenaufenthalt
G. D. Burchard	Differenzialdiagnose der Eosinophilie
H. Sudeck	Differenzialdiagnose pulmonaler Infiltrate
S. Ehrhardt	Anämie in den Tropen
S. Schmiedel	Abszesse
H. Ponstingl	Reisediarrhoe
J. Blessmann	Besonderheiten der HIV-Infektion in den Tropen

Seminar Reisemedizin und Public Health

H. Jäger	Reisemedizin
D. Wichmann	Flugreisemedizin und Tauchmedizin
S. Ehrhardt	Malaria-Prophylaxe
G. D. Burchard	Reiseimpfungen
H. Sudeck	Gifttiere
J. May	John Snow und die Cholera in London, Teil 1
J. May	John Snow und die Cholera in London, Teil 2
J. May	Sensitivität, Spezifität und prädiktiver Wert
S. Adjei	„Extended Programme of Immunization in the Tropics“
J. May	Bekämpfung der Malaria
B. Ebert	Erfahrungen mit der SARS-Epidemie

Training for Physicians
Fortbildungsveranstaltungen für Mediziner und medizinisches Fachpersonal

2004

28. Februar 2004
Fortbildung „Fieber nach Tropenaufenthalt“.

27. März 2004
Tag der Reisegesundheit
(Organisation: Reisemedizinisches Zentrum)

Oktober 2004
„Medizin in den Tropen“
Kurs für medizinisches Fachpersonal

2005

12. Februar 2005
Tag der Reisegesundheit
(Organisation: Reisemedizinisches Zentrum)
Ganztägige ärztliche Fortbildung

17. – 28. Oktober 2005
„Medizin in den Tropen“
Kurs für medizinisches Fachpersonal

31. Oktober – 04. November 2005
1. Aufbaukurs – Malaria und andere Blutparasitosen
Kurs für medizinisches Fachpersonal

29. – 30. Oktober 2005
Experten-Workshop Malaria
Forum Reisen und Medizin e.V.

18. – 20. November 2005
2. Refresher-Kurs Tropenmedizin

Seminar Programme

Seminarprogramm

Seminar Programme
Seminarprogramm
2004 – 2005

2004

Dr. Tim-Wolf Gilberger
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„Right Time, Right Place: Protein Trafficking and Invasion of *Plasmodium falciparum*" (12.01.04)

Dr. Serge Lebeque
Schering Plough, France
„Human Tumor Infiltrating Dendritic Cells: Revisiting their roles and their prognostic value" (19.01.04)

Dr. Stefan Busch
BioMed Central, London
"Open Access über BioMed Central" (22.01.04)

Dr. Jörg Andrä
Forschungszentrum Borstel
"Wirkmechanismen von antimikrobiellen Peptiden mit Bakterien und bakteriellen Komponenten" (26.01.04)

Prof. Dr. Frances Gotch
Imperial College London, Chelsea and Westminster Hospital, London
"Immunolocigal protection from HIV infection – HIV-specific immune responses on exposed but seronegative individuals" (02.02.04)

Dr. Stefan Geiger
Institut für Vergleichende Tropenmedizin und Parasitologie
LMU München
„Aspects and effects of helminthic infections" (05.02.04)

Dr. Eva Liebau
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„Glutathion-abhängige Entgiftungsprozesse in Nematoden" (13.02.04)

PD Dr. Hans-Michael Müller
EMBL Heidelberg
"Melanotic parasite encapsulation in the malaria mosquito *Anopheles gambiae* – how does it function?" (16.02.04)

Dr. Florian Heil
Institut für Medizinische Mikrobiologie
TU München
„Toll-like Rezeptoren 7 und 8 vermitteln die Immunerkennung von einzelsträngiger RNA" (19.02.04)

Dr. Peter Fischer
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„Bekämpfung humanpathogener Filarieninfektion: Charakterisierung von Molekülen der Filarien und ihrer *Wolbachia*-Endobakterien" (20.02.04)

Dr. Andreas Krüger
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„An investigation of the isolation of the Tukuyu focus of onchocerciasis from possible vector re-invasion" (23.02.04)

Dr. Simone Korten
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
"NKT cell help for novel poxvirus vaccination strategy against liver stage malaria" (27.02.04)

Dr. Qi Wang
Tularic Inc., San Francisco, USA
"CD4: thymus and beyond" (01.03.04)

Prof. Jabbar Ahmed
Forschungszentrum Borstel
"*Theileria* – host cell molecules: Relevances for host cell transformation and vaccine design" (01.03.04)

Dr. Jörg Heukelbach-Oliveira
Mandacaru Foundation, Brasilien
"Tungiasis in Brasilien" (08.03.04)

Dr. Stephan Becker
Institut für Virologie, Universität Marburg
„Der Nukleokapsidkomplex der Filoviren – ein Ziel für antivirale Therapie?" (25.03.04)

Christane Steeg
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„Methoden der Zellkultur" (31.03.04)

Prof. Dr. Klaus Lingelbach
Philipps Universität Marburg
„Protein trafficking in the *Plasmodium*-infected erythrocyte: a key event essential for host cell modification and parasite survival" (05.04.04)

Dr. Jacob Golenser
The Hebrew University of Jerusalem, Israel
"The effect of AmB derivatives on leishmaniasis and immune responses" (08.04.04)

Dr. Anton Aebischer
Department of Molecular Biology, MPI for Infection Biology, Berlin
"The rendez-vous of Dendritic cells with *Leishmania* spp. *in vitro* and *in vivo*" (19.04.04)

Prof. Dr. Matthias Leippe
Zoologisches Institut der Universität Kiel
"Ancient weapons for attack and defense: pore-forming proteins of pathogenic amoebae and their relatives in higher organisms" (26.04.04)

Prof. Dr. Gerhard Thiel
Technische Universität Darmstadt
"The viral encoded K^+ channel Kcv: a source of information on the molecular function of K^+ channels and on the role of ion conductances in viral infection" (03.05.04)

Dr. Matthias Wjst
Molecular Epidemiology Group, GSF National Research Center for Environment and Health, München
"Genetics of asthma and IgE in the Western World: What about research in Africa?" (10.05.04)

Dr. Alan F. Cowman
Walter and Eliza Hall Institute, Melbourne, Australien
"Molecular Insights into the Invasion of the Malaria Parasite" (24.05.04)

Prof. Rolf Hilgenfeld
Institut für Biochemie, Universität Lübeck
"Surviving hard times: The stringent response in bacteria" (25.05.04)

Prof. Dr. med. Werner Reutter
Institut für Biochemie u. Molekularbiologie
Charité-Universitätsmedizin, Berlin
"Biologische Bedeutung der N-Acylneuraminsäure, besonders ihrer N-Acyl-Analoga" (27.05.04)

Dr. Sem Saeland
Schering-Plough Laboratory for Immunological Research, Dardily, Frankreich
"Langerhans Cells in historical perspective" (07.06.2004)

Dr. Hüseyin Sirma
Heinrich-Pette-Institut für Experimentelle Virologie und Immunologie, Hamburg
"Molecular Dissection of the Infectious Life Cycle of Hepatitis B Virus" (14.06.04)

Monika Schofield
TUHH-Technologie GmbH (TuTech) EU Büro, Hamburg
"How to write a competitive EU proposal" (17.06.04)

Prof. Brigitte Autran
Université Paris VI Pierre et Marie Curie, Hospital Pitié-Salpêtrière, Paris
"Rationale and First results of two strategies of therapeutic immunisation against HIV" (21.06.04)

Jessica Carol Kissinger, Ph.D.
Center for Tropical and Emerging Global Diseases, University of Georgia, Athens
"Horizontal and Intracellular gene transfer in the Apicomplexa: The scope and functional consequences" (23.06.04)

Dr. Rory Post
The National History Museum, London
"Is natural interspecific hybridisation important in Medical Entomology?" (28.06.04)

Prof. Hagai Ginsburg
Hebrew University, Jerusalem
"How many channels are needed to account for the increased permeability of the *Plasmodium*-infected erythrocyte?" (09.08.04)

Dr. med. Jakob P. Cramer
Institut für Tropenmedizin Berlin, Charité
"Plasma nitric oxide levels, *iNOS* promoter variants, and severe malaria in Ghanaian children" (16.08.04)

Prof. Dr. Wilhelm Schwaeble
Department of Infection, Immunity and Inflammation
University of Leicester, UK
"Architecture, molecular composition and clinical manifestations of the lectin activation pathway of complement, an innate humoral defense system against microbial infection" (30.08.04)

Dr. Christiane Möcklinghoff
La Roche, Grenzach-Wyhlen
"Antiretroviral therapeutic regimens, HAART – present and future" (20.09.04)

Dr. Sandra Scheibelhofer
Universität Salzburg
„Next generation DNA-based vaccines" (27.09.04)

PD Dr. Sylke Müller
University of Dundee, Scotland
"Redox and antioxidant systems of the malaria parasite *Plasmodium falciparum*" (04.10.04)

Dr. Yaw Adu-Sarkodie
Kumasi, Ghana und London School of Hygiene and Tropical Medicine, London
"Are human trichomonads other than *Trichomonas vaginalis* involved in the aetiology of vaginal trichomoniasis?" (07.10.04)

Prof. Dr. Andreas Meyerhans
Universität des Saarlands, Homburg
"The non-clonal and transitory nature of HIV *in vivo*" (25.10.04)

Dr. Thorsten Hoppe
ZMNH Hamburg
"Regulation of the Myosin-Directed Chaperone UNC-45 in *Caenorhabditis elegans*" (01.11.04)

Prof. Boris Striepen
University of Georgia, Athens, USA
"Lateral Gene Transfers Shape the Evolution of Protozoan Parasites" (08.11.04)

Dr. Gordon Langsley
Institut Pasteur, Paris, France
"*Theileria* induced lymphocyte transformation is more a question of life than death" (15.11.04)

Dr. Klaus Brehm
Universität Würzburg
"Molecular analysis of host-helminth interactions: the fox-tapeworm *Echinococcus multilocularis* as a model system" (22.11.04)

Dr. Saskia de Ceuypere
Prins Leopold Institute of Tropical Medicine, Antwerp, Belgium
"Monitoring emergence and spreading of drug resistance among natural populations of *Leishmania*" (25.11.04)

Dr. Friedrich Frischknecht
Institut Pasteur, Paris, France
"Imaging motile malaria parasites during transmission" (03.12.04)

Prof. Dr. Norbert Müller
Universität Bern, AU
"Immunological and molecular aspects of antigenic variation in *Giardia lamblia*" (06.12.04)

Dr. Pete Bull
University of Oxford, UK
"The role of antibodies to *Plasmodium falciparum* erythrocyte surface
antigens in the development of naturally acquired immunity to malaria" (13.12.04)

2005

Prof. Dr. med. Sebastian Suerbaum
Med. Mikrobiologie und Krankenhaushygiene, Medizinische Hochschule Hannover
"*Helicobacter pylori* genetic variation – a pathogen's strategy for host adaptation and a new tool to study human migrations" (08.01.05)

Prof. Dr. Peter H. Seeberger
ETH Hönggerberg, Zürich, CH
"Automated Carbohydrate Synthesis and Sugar Arrays to Understand Disease Mechanism and Create Vaccine Candidates: Malaria, Leishmaniasis and HI as Examples" (24.1.05)

Prof. Eleanor Riley
London School of Hygiene and Tropical Medicine, London, UK
"T cell-mediated regulation of immune responses to malaria" (31.1.05)

Prof. Tony Holder
National Institute for Medical Research, London, UK
"Merozoites, antibodies and malaria" (07.02.05)

Prof. Dr. Ralf Schumann
Charité-Universitätsmedizin, Berlin
„Host-Pathogen Interaction, Toll-like receptors and disease susceptibility" (14.02.05)

Prof. Dr. Hans-Peter Beck
Swiss Tropical Institute, Basel, CH
"Expression of *Plasmodium falciparum* var-genes in naturally infected individuals" (21.02.05)

Prof. Dr. Christoph Grevelding
Justus-Liebig-Universität, Gießen
"*Schistosoma mansoni*: Sex and Drugs and Kinases" (28.02.05)

Dr. Stuart Ralph
Pasteur Institute, Paris, France
"Epigenetic regulation of antigenic variation in malaria" (14.03.05)

Prof. Herbert Schmitz, Dr. Christian Drosten, Prof. Paul Racz
Bernhard-Nocht-Institut für Tropenmedizin, Hamburg
„Tollwut bei Organspendern" (21.03.05)

PD Dr. Esther von Stebut
Johanne-Gutenberg-Universität, Mainz
„Die Bedeutung der Zytokine aus der IL-12 Familie für schützende Immunantworten in der Leishmaniose" (11.04.05)

Dr. rer. nat. Annette Kassen
Hochschule für Angewandte Wissenschaften, Hamburg
“International SRS control: analysis of European and non-European public health policies” (18.04.2005)

Prof. Dr. Thomas Winkler
Universität Erlangen
“T cell independent activation of virus specific memory B cells” (25.04.05)

Dr. Graham Clark
London School of Hygiene and Tropical Medicine, London, UK
“Is there a link between parasite genotype and outcome of infection with *Entamoeba histolytica*?” (02.05.05)

Prof. Marc Girard
Universität Paris
“The search for a HIV/AIDS vaccine:
Can we do better than nature?“ (20.05.05)

PD Dr. Friedemann Weber
Institut für Medizinische Mikrobiologie und Hygiene, Universität Freiburg
“SARS-coronavirus, bunyaviruses and the interferon system” (23.05.05)

Dr. Ursula Franke
Landesunfallkasse Hamburg
“Die neue Gefahrstoffverordnung”
– Übersicht
– Neue Pflichten (23.05.05)

PD Dr. Stephan Becker
Institut für Virologie, Universität Marburg
„Morphogenesis of Filoviruses“ (24.05.05)

Dr. Mark Wickham
University of British Columbia, Vancouver, Canada
“Hemolytic uremic syndrome: New virulence factors of enterohaemorrhagic *E. coli*” (30.05.05)

Dr. Ramon Flick
University of Texas Medical Branch, Galveston, USA
“Reverse genetics for hemorrhagic fever viruses: From basic research to antivirals” (06.06.05)

Dr. Stephan Günther
Bernhard-Nocht-Institut für Tropenmedizin
„Molecular epidemiology and reverse genetics of Lassa virus“ (07.06.05)

Dr. Bernardo Foth
Universität Genf
“Myosins and host cell invasion by apicomplexan parasites” (20.06.05)

Prof. Dr. Henning Scholze
Universität Osnabrück
„Hydrolasen und ihre Inhibitoren aus *Entamoeba histolytica*“ (20.06.05)

Prof. Andrew Hemphill
Universität Bern, CH
„The host-parasite relationship in neosporosis” (24.06.05)

Prof. Dr. med. Bodo Wanke
Instituto Oswaldo Cruz, Rio de Janeiro, Brasil
“Subkutane Mykosen und System-Mykosen” (18.07.05)

Dr. Jaqui Montegomery
University of Malawi, Blantyre
“Analysis of var expression in differentially sequestered populations of *Plasmodium falciparum* in fatal paediatric malaria” (12.09.05)

Dr. Till Voss
The Walter and Eliza Hall Institute of Medical Research, Australia
“There can only be one: Mutual exclusion in *P. falciparum* var gene expression” (19.09.05)

Dr. Tobias Spielmann
Queensland Institute of Medical Research, Australia
“Organisation of ETRAMPs and EXO-1 at the parasite-host cell interface of malaria parasites” (21.09.05)

Dr. Jochen Mattner
University of Chicago, USA
“Natural endogenous and exogenous ligands activating NKT cells” (26.09.05)

Dr. Johannes Herkel
UKE, Hamburg
“Immune regulation in liver” (10.10.05)

Dr. Sabine Mand
Institut für Medizinische Parasitologie, Universität Bonn
„Aktuelles zur Ultraschalldiagnostik und Doxycyclin-Therapie in der Filarienforschung” (21.11.05)

Dr. Alister Craig
Liverpool School of Tropical Medicine, Liverpool, UK
“Malaria cytoadherence and ICAM-1” (05.12.05)

Symposia and Meetings

Symposien und Arbeitstreffen

Symposia

2004

6. März 2004

6. Symposium für Tropendermatologie und Reisemedizin

Leitung: Prof. Dr. Gerd Burchard
Organisation: Dr. Maren Adler, Dr. Marcellus Fischer

- *Dr. M. Schwarz (Osteseeklinik Dierhagen):*
  „Die Entdeckung des Lepra-Bazillus, die Rolle der Dermatologie und viele Fragen“
- *T. von Stamm (Deutsches Aussätzigen Hilfswerk, Würzburg):*
  „Die Elimination von Lepra – ein virtuelles Phänomen“
- *Dr. I. Just (Lepramuseum Münster):*
  „Die Geschichte der Leprosorien in Deutschland“
- *PD Dr. K. Jankrist (Augsburg):*
  „Lepra in der Kunst des Mittelalters und der frühen Neuzeit“
- *Prof. Dr. P. Racz (BNI):*
  „Immunomorphologische Aspekte des Pathogenese der Lepra“
- *S. Kramme (BNI):*
  „Neue Aspekte der Lepra-Diagnose“
- *Dr. P. Traoré (Bamako, Mali):*
  „Die Situation der Lepra in Westafrika“
- *Dr. C. Bendick (Köln):*
  „Lepra in Südostasien – klinische Erfahrungen aus Kambodscha“
- *Prof. Dr. S. Talhari (Manaus, Brasilien):*
  „Klinische Aspekte der Lepra im brasilianischen Amazonasgebiet“
- *Dr. H. Sudeck (BNI):*
  „Therapie der Lepra“
- *E. Hisch (DAHW; Würzburg):*
  „Behandeln Sie mich nicht wie einen Aussätzigen“
- *Dr. J. König (DaHW, Würzburg):*
  „Das Deutsche Aussätzigen Hilfswerk – eine NGO mit Zukunft“

2005

April 28th/29th, 2005

6th Drug Development Seminar 2005 (Antiparasitic Chemotherapy)

Coordination: Dr. Martin Wiese, Dr. Mo Klinkert

Session 1: Biosynthetic pathways as drug targets

- *Mary Bendig (Drug Discovery Research, WHO/TDR):*
  „Drug discovery in the WHO/TDR: How we interact with biopharma companies“
- *Sylke Müller (University of Glasgow):*
  „Lipoic acid biosynthesis and the salvage in *Plasmodium falciparum* – potential targets for chemotherapy?“
- *Hassan Jomaa (Justus-Liebig University, Giessen):*
  „Oxygen-sensitive enzymes of the DOXP pathway as targets for new antimalarial drugs“
- *Jochen Wiesner (Justus-Liebig University, Giessen):*
  „NMR based structure refinement of DOXP reductoisomerase for the design of improved antimalarial drugs“
- *Ivo Tews (University of Heidelberg):*
  „High-resolution 3D structures of the homologous glutaminases Pdx2 and YaaE from *Plasmodium falciparum* and *Bacillus subtilis* involved in Vitamin B6 biosynthesis“

Session 2: Signalling pathways

- *Jeremy Mottram (University of Glasgow):*
  „Cyclin-dependent protein kinases as drug targets in trypanosomatids“
- *Christian Doerig (University of Glasgow):*
  „*Plasmodium* protein kinases: from database mining to drug discovery“
- *Stephanie Bolte (BNI, Hamburg):*
  „Parasite-dependent regulation of signal transduction pathways in *Plasmodium berghei*-infected hepatocytes“
- *Inga Melzer (BNI, Hamburg):*
  „LmxMPK1, a mitogen-activated protein (MAP) kinase homologue from *Leishmania mexicana* – a potential drug tragtet against Leishmaniasis?“
- *Ulrike Schubert (Novoplant, Gatersleben):*
  „Calcium signalling – a promising starting point for the development of new anticoccial drugs“
- *Kohelia Choudhury (BNI, Hamburg):*
  „A screen for genes that can transfer resistance to miltefosine in *Leishmania*“

Session 3: Chemotherapy of helminths

- *Donato Cioli (National Research Council of Italy):*
  „Antischistosomal drugs: broadening the spectrum of oxamniquine“
- *Achim Hörauf (University of Bonn):*
  „*Wolbachia* endosymbionts in filarial nematodes as targets for chemotherapy of filariasis with antibiotics“
- *Markus Perbandt (BNI, Hamburg):*
  „Structure of the major cytosolic glutathione S-transferase from the parasitic nematode *Onchcerca volvulus*“
- *Klaus Brehm (University of Würzburg):*
  „Receptor kinases and the MAP-kinase cascade of *Echinococcus multicularis* as possible targets for chemotherapy“
- *Susanne Hartmann (Humboldt-University Berlin):*
  „Antiinflammatory helminth products as a basis for drug design?“

Session 4: Redox enzymes and polyamines

- *Andreas Krasky (Akzo Nobel Intervet Innovation GmbH):*
  „Flavin-disulfide oxidoreductases as targets for the development of new antiparasitic drugs“
- *Christiane Nickel (Justus-Liebig University, Giessen):*
  „A novel peroxiredoxin of the malarial parasite *Plasmodium falciparum* has glutharedoxin-dependent peroxidase activity“
- *Monique Achoachere (Justus-Liebig University, Giessen):*
  „Characterization of the glyoxalases of the malarial parasite *Plasmodium falciparum* and the comparison with their human counterparts“
- *Marcel Deponte (Justus-Liebig University, Giessen):*
  „Biochemical properties of *Plasmodium falciparum* glutharedoxin-like proteins and comparison of *P. falciparum* and *T. gondii* 1-Cys peroxiredoxins“
- *Ingrid Müller (BNI, Hamburg):*
  „The plasmodial arginase – a potential drug target“
- *Kai Lürsen (BNI, Hamburg):*
  „3-Aminooxy-1-aminopropane and derivatives have an antiproliferative effect on cultured *Plasmodium falciparum* by decreasing intracellular polyamine concentrations“
- *Stefan Rahlfs (Justus-Liebig University, Giessen):*
  „Target identification: Plasmodial selenoproteins as possible drug targets“
- *Elisabeth Divioud-Charvet (Biochemie-Zentrum Heidelberg):*
  „A fluoro-analogue of the menadione derivative M5 is an efficient suicide substrate of both glutathione reductases from man and *Plasmodium falciparum*?“

Session 5: Parasite proteases

- *Graham Coombs (University of Glasgow):*
  „The *Leishmania* degradome: possibilities for drug targeting“
- *Michael Blackmann (National Institute for Medical Research, Mill Hill):*
  „Shooting the sheddases; malaria merozoite proteases as drug targets“
- *Yu-Shan Chia (BNI, Hamburg):*
  „Small peptide proteasome inhibitor in the development of novel anti-malarial agents“
- *Dietmar Steverding (University of East Anglia):*
  „Bloodstream formas of *Trypanosoma brucei* are particulary sensitive to inhibitors specifically targeting the proteasome trypsin-like activity“

October 21st, 2005

Clinical Virology and Emerging Pathogens

Symposium on the occasion of the 65th birthday of Prof. Herbert Schmitz, Head Department of Virology

- *A. D. M. E. Osterhaus (Rotterdam, The Netherlands):* „Emerging virus infections in a changing world“
- *J. Schmitz (Boston, USA):* „Diagnostic and pathogenomic laboratory markers of viral diseases in the models of CID and SARS“
- *M. Roggendorf (Essen):* „Immune control of SIV infection“
- *J. ter Meulen (Leiden, The Netherlands):* „Entwicklung therapeutischer Vakzinen für die chronische Hepatitis B“
- *H. Schmitz (BNI, Hamburg):* „Farewell lecture „Best of 25 years at the BNI“

Albert Osterhaus (left), Herbert Schmitz

Colleagues, friends and alumni enjoy the recollections of a veteran virologist
Kollegen, Freunde und ehemalige Mitarbeiter lauschen vergnügt den Erinnerungen eines verdienten Virologen

October 28th/29th, 2005

2. Malariatreffen

Programmkoordination: PD Dr. med. Jürgen May

Session 1: Pathophysiologie

- *Stephan Ehrhardt (Hamburg):*
  „Herzbeteiligung bei Malaria: Implikationen für das Flüssigkeitsmanagement?“
- *Christoph Hemmer (Rostock):*
  „Apoptose des Gefäßendothels bei Malaria und Sepsis“
- *Jakob Cramer (Hamburg):*
  „Severe malaria and innate immunity: Potential role of Toll-like receptors“
- *Peter Lackner (Innsbruck):*
  „Temporal and spatial profile of activated caspase-3 in experimental cerebral malaria“
- *Raimund Helbok (Innsbruck):*
  „Simplified MODS: ein neuer Ansatz zur Graduierung des Schweregrads einer *P. falciparum* Malaria“

Session 2: Parasitologie I

- *Rolf Fendel (Tübingen):*
  „Proteindegradation bei Plasmodien“
- *Tim Gilberger (Hamburg):*
  „Is simple good enough? The Golgi in the malaria parasite *P. falciparum*“
- *Jude Przyborski (Marburg):*
  „Life on an intracellular island: The strange case of *P. falciparum*“

Session 2: Parasitiologie II

- *Volker Heussler (Hamburg):*
  „Parasite-host cell interaction during late stages of *P. berghei* infection of hepatocytes“
- *Hassan Jomaa (Giessen):*
  „Parasitäre Enzyme als Ansatzpunkte der Therapie von Plasmodien“
- *Ayman Khattab (Hamburg):*
  „Surprising new turns in RIFIN traffic“
- *Carsten Wrenger (Hamburg):*
  „Synthese von Vitamin B1 und B6 in *P. falciparum*“

Session 3: Epidemiologie

- *Hans-Peter Beck (Basel):*
  „*var* gene expression dynamics in *P. falciparum*“
- *Ingrid Felger (Basel):*
  „Dynamics of *P. falciparum* infections“
- *Robin Kobbe (Hamburg):*
  „Infektionsdynamik von *P. falciparum* in den ersten Lebensmonaten bei Kindern aus einem holoendemischen Gebiet“

Session 4: Immunologie

- *Michael Saeftel (Bonn):*
  „A previous infection with filaria (*Litomoisoides sigmodontis*) protects against inescapable death through cerebral malaria in *P. berghei* (ANKA) infected C57BL/6 mice“
- *Thomas Jacobs (Hamburg):*
  „Beteiligung von CTLA-4 an der Immunregulation im Verlauf der Malaria“
- *Jürgen Kun (Tübingen):*
  „Malaria and Microarrays“
- *Nadine Schreiber (Hamburg):*
  „Immunantwort gegen *P. falciparum* Rifin-Antigen bei Malaria“

Session 5: Malariakontrolle

- *Claudi Beyersmann & Olaf Müller:*
  „Local concepts, health-seeking behaviour and patterns of traditional malaria treatment in rural Burkina Faso“
- *Frank Mockenhaupt (Berlin):*
  „Marker der Medikamentenresistenz in Nordghana“
- *Gabriele Pradel (Würzburg):*
  „Indentifying novel drug and vaccine targets in the malaria pathogen *P. falciparum*“

Session 6: Wirtsgenetik

- *Christian Timmann (Hamburg):*
  „Genetische Einflussfaktoren der Plasmodieninfektion in einer longitudinalen Studie aus Ghana“
- *Angelica Boldt (Tübingen):*
  „MBL2 diplotypes generating a low level of mannose binding lectin are associated with higher cytokine levels and protection against the most severe outcomes of malaria in Gabon“
- *Christopher Intemann (Hamburg):*
  „Assoziationen von Genvarianten aus der Chromosomenregion 5q31 mit der Infektionsdynamik von *P. falciparum*“

Session 7: Therapie und Prophylaxe

- *August Stich (Würzburg):*
  „Intensivtherapie der schweren Falciparum Malaria – ein Platz für den Einsatz von aktiviertem Protein C“
- *Peter Meissner & Olaf Müller (Heidelberg):*
  „Methylene blue for malaria – latest results from multidisciplinary drug development project“
- *Thomas Jelinek (Berlin):*
  „Einfluß der Medikation auf Therapie- und Liegedauer bei unkomplizierter Malaria tropica (TropNetEurope)“

Meetings of Cooperative Scientific Projects
Arbeitstreffen im Rahmen von Verbundprojekten

May 6th, 2004

EU Consortium:
„Development and commercial production of standardized PCR-assays for detection of hemorrhagic fever viruses and variola virus and their implementation in the diagnostic service of EU P4 laboratories“
(VHF/ Variola PCR)
Coordination: Stephan Günther, BNI

Partners:
- *S. Günther & C. Drosten*, BNI, Hamburg, Gemany
- *S. Becker*, Philipps University Marburg, Germany
- *V. Deubel*, Institut Pasteur, Paris, France
- *G. Lloyd*, Health Protection Agency, Porton Down, UK
- *D. Brown*, Health Protection Agency, London Colindale, UK
- *A. Lundkvist*, Swedish Institute for Infectious Diseases Control, Sweden
- *H. Meyer*, Institute for Microbiology of the German Armed Forces, Germany

May 7th, 2004

EU Consortium:
EURONET-P4 (SANCO) project:
„Development of a network of the existing European P4 laboratories“
Coordination: Vincent Deubel (Lyon), now Giuseppe Ippolito (Rome)

Partners:
- Philipps University, Marburg, Germany
- Swedish Institute for Infectious Diseases Control, Sweden
- Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
- Health Protection Agency, UK
- National Institute for Infectious Diseases IRCCS „L. Spallanzani“, Rome, Italy

June 18th/19th, 2004

5th PAMVAC Meeting:
„Development of Vaccine against pregnancy-associated malaria“
Coordination: Mo Klinkert, BNI

Partners:
- *David Arnot,* University of Edinburgh, United Kingdom
- *Mats Wahlgren,* Karolinska Institute, Stockholm, Sweden
- *Graham A. Bentley*, Institut Pasteur, Paris, France
- *Philippe Deloron,* Faculté des Sciences Pharmaceutiques, Paris, France
- *Lars Hviid,* Centre for Medical Parasitology, Copenhagen, Denmark

December 5th/6th, 2004

EU Consortium: „Mucosal Vaccines against Human and Simian Immunodeficiency Virus based on Dendritic Cells“ (MUVADEN)
Coordination: Paul Racz, BNI

Partners:
- *R. Steinman & C. Trumpfheller*, Rockefeller University, New York, USA
- *K. Überla*, Ruhr-Universität, Bochum
- *C. Stahl-Henning*, German Primate Center, Göttingen
- *M. Dietrich & H. Stoiber*, Institut für Hygiene, Insbruck
- *K. Tenner Racz & P. Racz*, BNI Hamburg
- *G. Pozzi*, Universitá degli Studi di Siena, Italia
- *R. Ignatius & M. Eisenblätter*, Charité, Berlin

Staff Activities

Aktivitäten der Mitarbeiter

Staff Activities
Aktivitäten der Mitarbeiter

Dr. Jörg Blessmann

Clinical Department

Invited Lecturer

7. Tübinger Tag der Reisemedizin (03/2004)
Bremer Tag der Reisemedizin (09/2004)

PD Dr. Norbert Brattig

Tropical Medine Section

Memberships in Committees and Advisory Boards

Habilitation Commission, University of Leipzig (2004)

Teaching

Zoology, Faculty of Biology, University of Hamburg

Invited Lecturer

University of Hohenheim (02/2004)
IX. European Multicolloquium of Parasitology (EMOP IX), Valencia, Spain (07/2004, keynote speaker)
University of Mainz (06/2005)

Dr. Minka Breloer

Medical Microbiology Section

Teaching

Immunology, Faculty of Biology/Chemistry and Medicine, University of Hamburg

PD Dr. Iris Bruchhaus

Parasitology Section

Offices and Posts

Ombudsfrau für Fälle wissenschaftlichen Fehlverhaltens; BNI (since 2000)
Strahlenschutzbeauftragte (Parasitology Section); BNI (since 2001)

Teaching

Zoology/Molecular Biology, Faculty of Biology, University of Hamburg

Invited Lecturer

University of Göttingen, Seminar (07/2004)

Prof. Dr. Gerd Dieter Burchard

Clinical Department

Membership in Committees and Advisory Boards

German Society for Tropical Medicine and International Health (Treasurer, since 1993)
Panel “Travel Medicine”, German Society for Tropical Medicine and International Health (since 1993)
Coordinator Panel ”Broad Outline Development”, German Society for Tropical Medicine and International Health (since 1997)
Scientific Advisory Board, Deutsche Akademie der Flug- und Reisemedizin (since 1997)
Scientific Advisory Board, Forum Reisen und Medizin e.V. (since 2001)
Extraordinary Member, Arzneimittelkommission der Deutschen Ärzteschaft (since 1994)
Examination Board, Ärztekammer Hamburg (since 2003)

Editorial Activities

Journal of Travel Medicine

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer
University Hospital Schleswig-Holstein, Lübeck (01/2004)
Ärztekammer Hamburg (02/2004)
Reisemedizinischer Arbeitskreis, Marburg (02/2004)
Bund Deutscher Internisten, Berlin(03/2004)
Deutsche Gesellschaft für Wehrmedizin und Wehrmedizin, Hannover (04/2004)
Kassenärztliche Vereinigung, Hamburg (06/2004)
Potsdamer Gastroenterologisches Seminar (09/2004)
7. Reisemedizinisches Update, Firma Aventis, Hamburg (10/2004)
Schifffahrtsmedizinisches Institut der Marine (11/2004)
MEDICA, Düsseldorf (11/2004)
Rahmenprogramm 7. Deutscher Interdisziplinärer Kongress für Intensiv- und Notfallmedizin (12/2004)
Ärztlicher Verein, Fortbildungsakademie Hamburg (12/2004)
Organizer and Chairman
Chairman, Ärztlicher Verein, Ärztekammer Hamburg (since 2004)
130. Jahrestagung der Nordwestdeutschen Gesellschaft für Innere Medizin, Hamburg (02/2004)

PD Dr. Joachim Clos

Parasitology Section
Memberships in Committees and Advisory Boards
Hamburger Kommission für Fragen der Gentechnik (since 2002)
Teaching
Zoology/Molecular Biology, Faculty of Biology, University of Hamburg
Invited Lecturer
University of Porto (04/2004)
EMBO workshop “The Hsp90 chaperone machine”, Geneva (09/2004)

Dr. Jakob P. Cramer

Clinical Department
Teaching
Tropical Medicine, Charité, University Medical Centre, Berlin

Dr. Christian Drosten

Medical Microbiology Section
Awards
GlaxoSmithKline Award for Clinical Infectiology of the German Society for Infectiology (06/2004)
Abbott Diagnostics Award of the European Society for Clinical Virology (09/2004)
BioMerieux Diagnostikpreis der Deutschen Gesellschaft für Hygiene und Mikrobiologie (09/2004)
Postdoktorandenpreis der Robert-Koch Stiftung (11/2004)
European Junior Award de la Societé des Sciences de la Santé (11/2005)
Bundesverdienstkreuz am Bande vergeben durch den Bundespräsidenten (12/2005)
Memberships in Committees and Advisory Boards
Arbeitsgruppe Lageerkundung, Bundesamt für Bevölkerungsschutz, RKI (since 2003)
Mitglied im Expertennetzwerk „Biologische Gefahren“, Bundesamt für Bevölkerungsschutz, RKI (since 2003)
External Advisor, WHO Laboratory Twinning Partnership Initiative (since 2004)
Scientific Advisory Board, German Society for Infectiology (since 06/2005)
Gewähltes Mitglied der Jungen Akademie (since 09/2005)
Teaching
Virology, Faculty of Medicine, University of Hamburg
Invited Lecturer
University of Leuven, Belgium (02/2004)
Annual Meeting of the Society of Virology (03/2004, keynote speaker)
German Society for Infectiology, ConVir, Regensburg (05/2004)
Symposium “Threat of Infection“ Wissenschaftsgemeinschaft Leopoldina (07/2004)
Symposium “Molecular and Clinical Aspects of SARS” Foundation Ramon Areces (10/2004)
Symposium “Emerging respiratory diseases” Foundation Merieux (11/2004)
Annual Meeting of the German Society for Virology, Hannover (03/2005)
Annual Meeting of the European Society for Clinical Virology, Geneva (04/2005)
Annual Meeting of the German Society for Infectiology and Tropical Medicine, Hamburg (06/2005)

Organizer and Chairman
Annual Meeting of the German Society for Internal Medicine (03/2004)

Dr. Stephan Ehrhardt

Clinical Department
Teaching
Faculty of Medicine, University of Hamburg
Epidemiology in the tropics, University of Göttingen
Highly Contagious Infections, Hamburger Feuerwehr
Refresher Course Tropical Medicine, BNI Hamburg
Invited Lecturer
Akademie für medizinische Fort-und Weiterbildung der Ärztekammer Schleswig-Holstein (11/2004)

Dr. Peter Fischer

Medical Microbiology Section
Habilitation und Venia Legendi, Fachbereich Medizin, University of Hamburg (07/2004)
Invited Lecturer
University of Würzburg (06/2004)
International Livestock Research Institute, Nairobi, Kenya (09/2004)
School and Medicine, Infectious Diseases Devision, Washington University, St. Louis, USA (10/2004)
Organizer and Chairman
1st Asian Congress of Parasitology and Tropical Medicine, Kuala Lumpur, Malaysia (03/2004)
Joint Filarial/Schistosomal Genome Meeting at TIGR (Scientific Advisory Board), Rockville, Maryland, USA (08/2004)

Prof. Bernhard Fleischer

Medical Microbiology Section
Professor (C4) for Tropical Medicine, Faculty of Medicine, University of Hamburg
Director of the Institute of Immunology, University Hospital Hamburg-Eppendorf (UKE) (since 2002)
Membership in Committees and Advisory Boards
Scientific and Technical Advisory Committee (STAC), UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) (since 2003)
Governing Board, German Society for Tropical Medicine and International Health (since 2001)
Advisory Board, German Society for Immunology (since 1992)
Deutsche Akademie der Naturforscher Leopoldina (since 1995)
Advisory Board, Institute for Medical and Pharmaceutical Examination Regulations (since 1991)
Scientific Advisory Board, German Primate Research Centre, Göttingen (since 1999)
Scientific Advisory Board, Centre for Infectious Diseases, University of Würzburg (since 2001)
Board of Trustees, Landesbetrieb Krankenhäuser Hamburg (since 2002)
R&D Expert Group on Countering Bioterrorism, European Commission (since 2002)
Commission on Infectious Diseases, European Academies' Science Advisory Council (EASAC) (since 2005)
Ex officio-member, Scientific Advisory Board, Robert Koch Institutes (since 1999)
Board of Directors, Werner Otto Foundation (since 2003)
Selection Committee, Alexander von Humboldt Foundation (since 2005)
Editorial Activities
Medical Microbiology and Immunology
International Journal of Medical Microbiology
Tropical Medicine and International Health
Teaching
Immunology, Faculty of Medicine and Chemistry, University of Hamburg
Invited Lecturer
Annual Meeting of the Sanitary Commando of the German Armed Forces (03/2004)
Roche AG, Basel, Switzerland (05/2004)
NGRI, Hyderabad, India (09/2004)
Ärztekammer Hamburg (2005)
Joint Workshop of German and Indian Societies of Immunology, Delhi, India (02/2005)
Leibniz Forum, Hamburg (02/2005)
Leibniz Forum, Brussels (09/2005)
European Molecular Biology Laboratory (EMBL), Monterotondo, Italy (11/2005)

Organizer and Chairman
Symposium on Infectious Diseases, Deutsche Akademie der Naturforscher Leopoldina (07/2004)
Workshop on North-South-Cooperation, Volkswagen Foundation, Accra, Ghana (keynote speaker, 04/2004)
International Seminar on water and air and food-borne diseases, awareness and control, Hyderabad, India (keynote speaker, 09/2004)
International Colloquium on Tuberculosis and Buruli Ulcer, Cotonou, Bénin (12/2005)

Prof. Dr. Rolf Garms

Medical Microbiology Section
Membership in Committees and Advisory Boards
Basic Health Services, Fort Portal Uganda "Onchocerciasis vector elimination in Western Uganda" and its evaluation
Invited Lecturer
43th Meeting of the German Dermatological Society, Dresden (04/2005)
Microbiology Summer School, European Academy of Dermatology and Venerology, Vienna, Austria (07/2005)

Dr. Tim-Wolf Gilberger

Parasitology Section
Emmy Noether Fellow (DFG)
Invited Lecturer
University of Blantyre, Welcome Trust Centre, Liverpool, England (11/2004)
ITREID/SBRI, Asian workshop, Jawaharlal Nahru University, New Delhi, India (06/2005)
NCMLS, Department of Biology, Nijmegen, Netherlands (06/2005)
University of Glasgow, Scotland (12/2005)

PD Dr. Stephan Günther

Parasitology Section
Membership in Committees and Advisory Boards
International Scientific Council of the BSL-4 laboratory in Lyon, Lyon, France (since 2004)
Teaching
Tropical Medicine, Faculty of Medicine, University of Hamburg
Invited Lecturer
University Medical Centre, Würzburg (03/2004)
Workshop of the VW Foundation "Communicable disease research in Sub-Saharan Africa – from the African bench to patients and populations" Accra, Ghana (04/2004)
3rd European Conference on Viral Disease – ConVir 2004, Regensburg (05/2004)
6th Meeting of the R&D Expert group on countering the effects of biological and chemical terrorism, European Commission, Brussels, Belgium (06/2004)
II. Fortbildungsveranstaltung des Medizinischen Dienstes der Krankenversicherer Hamburg" (06/2004)
University of Erlangen-Nürnberg (10/2004)
Meeting of the Scientific Advisory Committee, Chiron Corporation, London, UK (11/2004)

PD Dr. Volker Heussler

Parasitology Section
Awards
Eduard-Adolf-Stein-Preis, University of Bern, Switzerland (11/2005)
Teaching
Faculty of Biology/Chemistry, University of Hamburg
Invited Lecturer
Institute Pasteur, Paris, France (01/2005)
University of Heidelberg (05/2005)
University of Glasgow, Scotland (11/2005)
University of Bern, Switzerland (11/2005)
Symposium "Apoptosis and protozoan parasites", British Society of Parasitology, London (11/2005, keynote speaker)
Symposium "Liver stage of *Plasmodium*", American Society of Tropical Medicine and Hygiene, Washington, USA (12/2005)

Prof. Rolf Horstmann

Tropical Medicine Section

Professor (C4) for Tropical Medicine, Faculty of Medicine, University of Hamburg

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

University of Rostock (07/2004)
Ärztekammer Hamburg (03/2005)
University of Kiel (07/2005)
Rostock-Brown Universities Summer School, University of Rostock (07/2005)
Annual Meeting of the German Genetics Society, GBF Braunschweig (09/2005)
GSK Malaria Experten-Workshop, BNI Hamburg (10/2005)

Organizer and Chairman

Annual Meeting of the German Society for Infectiology and Tropical Medicine, Hamburg (06/2005)

Dr. Thomas Jacobs

Medical Microbiology Section

Teaching

Immunology, Faculty of Biology/Chemistry, University of Hamburg

Invited Lecturer

University of Salzburg, Austria (03/2004)
University of Bremen (05/2004)
University of Kiel (11/2004)
Institute for Immunology, Charité, Berlin (02/2005)
Ärztliche Weiterbildung, Itzehoe (04/2005)
Technical Acadamy of Sciences, Prag (09/2005)
University of Essen (12/2005)

Organizer and Chairman

Annual Meeting of the German Society of Parasitology (DGP), Würzburg (03/2004)

PD Dr. Mo Klinkert

Tropical Medicine Section

Membership in Committees and Advisory Boards

Scientific Review Committee, EDCTP Training Awards (since 11/2005)

Invited Lecturer

Institute for Medical Research, Kuala Lumpur, Malaysia (04/2004)
Karolinska Institute, Stockholm, Sweden (03/2005)
University of Helsinki, Finland (11/2005)

Organizer and Chairman

5th PAMVAC meeting, Hamburg (04/2004)
6th Drug Development Seminar: Antiparasitic Chemotherapy, Hamburg (04/2005)

Dr. Zita Krnajski

Parasitology Section

Awards

Gerhard Piekarski Award, German Society for Parasitology (2004)
Best Thesis Award, Vereinigung der Freunde des Tropeninstituts e.V. (2004)

Dr. Andreas Krüger

Parasitology Section

Membership in Committees and Advisory Boards

External Advisor, “Regierungspräsidium Freiburg, Abteilung Umwelt”, Rathaus Weisweil (04/2005)

Dr. Beate Kümmerer

Medical Microbiology Section

Teaching

Virology, Faculty of Medicine, University of Hamburg

PD Dr. Eva Liebau

Parasitology Section

Teaching

Zoology/Molecular Biology, Faculty of Biology, University of Hamburg

Invited Lecturer

University of Muenster (02/2004)
Humboldt-University, Berlin (06/2004)
University of Kiel (09/2004)

Dr. Ute Lippert

Clinical Department

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

Ärztekammer Bad Segeberg (04/2004)
Ärztekammer Osterholz Scharmbeck (05/2004)
CRM Hannover und Hamburg (04, 10/2004)
Ärztekammer Hamburg (01/2004)
Fortbildung Hanseärzte Hamburg (08/2004)

Dr. Kai Lüersen

Parasitology Section

Teaching

Parasitology, Faculty of Biology, University of Hamburg

Invited Lecturer

Workshop on “Protozoan Pathogens”, Indo-Swedish Research Partnership, Goa, India (12/2005)

PD Dr. Jürgen May

Tropical Medicine Section

Membership in Committees and Advisory Boards

Data Safety Monitoring Board, Hôpital Albert Schweitzer, Lambaréné, Gabon (since 2003)
Arbeitskreis “Malaria-Therapie”, Sektion “Antiparasitäre Chemotherapie”, Paul-Ehrlich-Gesellschaft (since 2003)

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg
Tropical Medicine, Faculty of Medicine, Charité, University Medical Centre, Berlin

Invited Lecturer

Annual Meeting of the German Society for Infectiology and Tropical Medicine, Hamburg (06/2005)
4th Pan-African Malaria Conference, Multilateral Initiative for Malaria (MIM), Yaoundé, Cameroon (11/2005)

Organizer and Chairman

1st Malaria Meeting, Paul Ehrlich Society (10/2004)
2nd Malaria Meeting, Paul Ehrlich Society and DTG, Hamburg (11/2005)

Prof. Dr. Christian G. Meyer

Tropical Medicine Section

Editorial Activities

Tropical Medicine and International Health
Flug- und Reisemedizin

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

IX. Symposium “Reise-und Impfmedizin” des Auswärtigen Amtes, Berlin (05/2004)
University Medical Centre Hamburg Eppendorf (06/2004 and 10/2004)
MEDICA 2004, Düsseldorf (11/2004)
MEDICA 2005, Düsseldorf (11/2005)
Ärztekurs, Schifffahrtsmedizinisches Institut der Marine, Kiel (12/2005)

Dr. Sonja Niknafs

Medical Microbiology Section

Awards

MEDAC Dissertationspreis für Immunologie (2005)

Prof. Dr. Paul Racz

Tropical Medicine Section

Awards

"Bundesverdienstkreuz am Bande" verliehen durch den Bundespräsidenten (12/2005)

Membership in Committees and Advisory Boards

Scientific Advisory Board "Steering Committee Competence Network, HIV/AIDS" Germany (since 2001)

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

Mucosal Vaccines for Poverty Related Diseases, Siena, Italy (03/2004)
Clinical Vaccine Trials, Correlates of Protection, Göteborg, Sweden (05/2004)
German HIV-Net Symposium, Bochum, Germany (07/2004)
Charité, University Medical Centre, Berlin, Germany (06/2004)
10th German and 16th Austrian AIDS Congress, Vienna, Austria (06/2005)

PD Dr. Uwe Ritter

Medical Microbiology Section

Habilitation, Friedrich-Alexander-University Erlangen-Nürnberg (01/05)
Umhabilitation, University of Hamburg (07/2005)

Teaching

Immunology, Faculty of Biology/Chemistry, University of Hamburg
Lectures at the University of Salzburg, Austria

Invited Lecturer

University of Salzburg, Austria (02, 11/2005)
MediGen, Martinsried, Munich (07/2005)

Dr. Stephan Schmiedel

Clinical Department

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

Fortbildung Hanseärzte Hamburg (08/2004)
Lufthansa, Fliegerarztlehrgang Seeheim (10/2004)
Bremer Reisemedizinisches Kolloquium, Krankenhaus Rotenburg/Wümme (09/2004)

Prof. Dr. Herbert Schmitz

Medical Microbiology Section

Membership in Committees and Advisory Boards

Scientific Advisory Board, Eurpean Society for Clinical Virology (since 2000)
Scientific Advisory Board, European Network on Imposed Viral Diseases (ENIVD) (since 2000)
Advisor, BSL3 Laboratory, Lissabon, Portugal (2005)
Advisor, German Society for Organ Transplantation (2005)
Medical Advisor, Olympic Games, Athens, Greece (2004)

Teaching

Virology, Faculty of Medicine, University of Hamburg

Invited Lecturer
Media workshop BMBF, Hamburg (03/2004)
GASAG Meeting, Berlin (04/2004)
Medical Society, Düsseldorf (04/2004)
ConVir, German Society for Infectious Diseases, Munich (05/2004)
SMK Meeting, Swedish Institute for Infectious Disease Control, Stockholm, Sweden (05/2004)
University of Marburg (06/2004)
Africa working party, Hamburg (06/2004)
OECD Meeting, Frascati, Italy (09/2004)
Expert Network Biological Dangers, Göttingen (11/2004)
Robert Koch Institute, Berlin (11/2004)
Foreign Office, Berlin (11/2004)
Institute for Virology, Pavia, Italy (12/2004)
University of Leipzig (04/2005)
ENIVD Meeting, Rome, Italy (06/2005)
Annual Meeting of the German Society for Infectiology and Tropical Medicine, Hamburg (06/2005)
Dt. Hämophilieverein, Frankfurt Airport (11/2005)
Organizer and Chairman
Winter Meeting of the European Society for Clinical Virology, Copenhagen, Denmark (01/2004)

Prof. Dr. Justus Schottelius

Parasitology Section
Teaching
Protozoology, Faculty of Biology, University of Hamburg
Medical Protozoology, General Hospital St. Georg, MTA School, Hamburg
Infectiology, Institute for Maritime Medicine of the German Navy, Kronshagen

Dr. Michael Schreiber

Medical Microbiology Section
Teaching
Tropical Medicine, Faculty of Medicine, University of Hamburg

Dr. Hinrich Sudeck

Clinical Department
Membership in Committees and Advisory Boards
Scientific Advisory Board “Arbeitsgemeinschaft Ultraschall der Hamburger Internisten” (since 2003)
Examination Board, Ärztekammer Hamburg (since 2002)
Examination Board, Ärztekammer Niedersachsen (since 2003)
Kammerversammlung der Ärztekammer Hamburg (since 2002)
Scientific Advisor, Institut für Reisemedizin, Köln (since 2003)
Teaching
Tropical Medicine, Faculty of Medicine, University of Hamburg
Invited Lecturer
Ärztekammer Hamburg (02/2004)
Ärztekammer Hamburg & IFRM Köln (02/2004)
Annual Meeting of the Society of Tropical Dermatology, BNI (03/2004)
Deutsche Akademie für Flug- und Reisemedizin, Frankfurt a.M. (03/2004)
Krankenhaus Alten Eichen, Hamburg (06,12/2004)
University of Lübeck (06/2004)
University of Kiel (10/2004)
Gastro – up date, AK Altona, Hamburg (12/2004)
Organizer and Chairman
Annual Meeting of the German Society for Tropical Medicine and International Health (09/2004)

Nicole Struck

Parasitology Section
Awards
Endeavour Australia Student Award, Australian Government, Department of Education, Science and Training (2004)

Prof. Dr. Egbert Tannich

Parasitology Section

Professor (C4) for Molecular Parasitology/Tropical Medicine, Faculty of Medicine, University of Hamburg

Membership in Committees and Advisory Boards

Scientific Advisory Board, Pathogenomics, Würzburg (since 2002)
Qualitätssicherungskommission der DGHM,: Bereich Ringversuche Parasitologie (since 2003)
Scientific Advisory Board, German Society for Parasitology (since 2004)
Scientific Advisory Board, German Society for Tropical Medicine (since 2005)
Scientific Advisor, Institute for Standardisation and Documentation in Medical Laboratories (since 2005)

Editorial Activities

Molecular and Biochemical Parasitology
Parasitology International
Parasitology Research

Teaching

Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

University of Göttingen, Public Lecture (02/2004)
Max Planck Institute for Infection Biology, Berlin, Seminar (04/2004)
Symposium “Genomics and biology of the amitochondriates” Marine Lab., MA, USA (09/2004)
Deutsche Forschungsgemeinschaft, Bonn (09/2004)
Symposium der Qualitätssicherungs-Kommission, 56. Annual Meeting DGHM (09/2004)
Hygiene-Tagung Trier (05/2005)
Symposium Qualitätssicherung im Medizinischen Labor, Berlin (06/2005)
DELAB-Fachtagung, Mainz (06/2005)
Summer School Biology of Parasitism, Woods Hole, MA, USA (08/2005)
39th Annual Meeting of the Austrian Society for Tropical Medicine an Parasitology, Vienna (11/2005)

Organizer and Chairman

EMBO workshop on Pathogenesis of amoebiasis: from genomics to disease, En Ghedi, Israel (11/2004)

Dr. Klara Tenner-Racz

Tropical Medicine Section

Awards

“Bundesverdienstkreuz am Bande” verliehen durch den Bundespräsidenten (12/2005)

Membership in Committees and Advisory Boards

Steering Committee “TIP-VAC”, EU project (since 2005)

Teaching

Course in Tropical Medicine, BNI Hamburg

Invited Lecturer

Mucosal Vaccines for Poverty Related Diseases, Siena, Italy (03/2004)
Clinical Vaccine Trials, Correlates of Protection, Göteborg, Sweden (05/2004)
Deutsches HIV-Net Symposium, Bochum, Germany (07/2004)
Charité, University Medical Centre, Berlin, Germany (06/2004)

Organizer and Chairman

10. Deutscher und 16. Österreichischer AIDS Kongress, Vienna, Austria (06/2005)

Prof. Dr. Rolf D. Walter

Parasitology Section

Membership in Committees and Advisory Boards

Management Committee Member “COST Action B22, European Commission” (since 2003)

Editorial Activities

Tropical Medicine and International Health
Molecular and Biochemical Parasitology
Journal Parasitic Diseases

Teaching

Parasitology, Faculty of Biology, University of Hamburg

Organizer and Chairman

6th Drug Development Seminar: Antiparasitic Chemotherapy, DPG (04/2005)

Dr. Martin Wiese

Parasitology Section

Teaching

Biochemistry, Faculty of Chemistry, University of Hamburg
Tropical Medicine, Faculty of Medicine, University of Hamburg

Invited Lecturer

Deutsche Forschungsgemeinschaft, Bonn (03/2004)
Medical University of Hannover (04/2004)
50th Annual Meeting FK-DVG, Hamburg (09/2004)
University of Glasgow, Scotland (11/2004)
University of Dundee, Scotland (12/2004)
University of Lübeck (07/2005)
Deutsche Forschungsgemeinschaft, Marburg (03/2005)
Fachhochschule Senftenberg (11/2005)

Organizer and Chairman

6th Drug Development Seminar, Antiparasitic Chemotherapy, BNI (04/2005)

Dr. Carsten Wrenger

Parasitology Section

Invited Lecturer

University of Pretoria, South Africa (01/2005)

Publications 2004 – 2005

Publikationen 2004 – 2005

Publications 2004

Book chapters and monographs

Drosten C (2004). Detection of SARS-Coronavirus in the LightCycler by 5'-nuclease real-time RT-PCR. In: Rapid Cycle Real-Time PCR – Methods and Applications. C. Wittwer, M. Hahn and K. Kaul, Eds. Springer, Heidelberg.

Drosten C (2004). Viral hemorrhagic fevers – Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. In: Encyclopedia of Diagnostic Proteomics and Genomics. Marcel Dekker, New York.

Drosten C, Kummerer BM, Schmitz H and Gunther S (2004). Molecular diagnostics of viral hemorrhagic fevers. In: Handbook of Viral Bioterrorism and Biodefence. E. De Clercq and E. Kern, Eds. Elsevier, Amsterdam.

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Peer-reviewed articles

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Berger A, Drosten C, Doerr HW, Sturmer M and Preiser W (2004). Severe acute respiratory syndrome (SARS)--paradigm of an emerging viral infection. J Clin Virol 29 (1): 13-22.

Birkholtz LM, Wrenger C, Joubert F, Wells GA, Walter RD and Louw AI (2004). Parasite-specific inserts in the bifunctional S-adenosylmethionine decarboxylase/ornithine decarboxylase of Plasmodium falciparum modulate catalytic activities and domain interactions. Biochem J 377 (Pt 2): 439-48.

Brattig NW (2004). Pathogenesis and host responses in human onchocerciasis: impact of Onchocerca filariae and Wolbachia endobacteria. Microbes Infect 6 (1): 113-28.

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Appendix

Anhang

Chronicle Bernhard Nocht Institute 2004 – 2005
Chronik Bernhard-Nocht-Institut 2004 – 2005

2004

11. Februar 2004
Kuratoriumssitzung.

12. Februar 2004
Besuch des Ersten Bürgermeisters der Freien und Hansestadt Hamburg, Ole von Beust.

28. Februar 2004
Tropenmedizinisches Seminar für niedergelassene Ärzte: „Fieber nach Tropenaufenthalt".

06. März 2004
7. Symposium für Tropendermatologie und Reisemedizin über „Mykosen und Mykobakteriosen – in den Tropen und zu Hause". Organisiert in Zusammenarbeit mit der *Society for Dermatology in the Tropics* (Programm S. 132).

27. März 2004
Tag der Reisegesundheit
(Organisation: Reisemedizinisches Zentrum).

05. April – 30. Juni 2004
Diplomkursus für Tropenmedizin (s. auch S. 116/117).

07. April 2004
Besuch MdB Jürgen Klimke, CDU.

13. April 2004
Besuch Senator Jörg Dräger, PhD
(Behörde für Wissenschaft und Gesundheit).

29. April 2004
Girls' Day im Tropeninstitut.

February 11th, 2004
Board of Directors meeting.

February 12th, 2004
Ole von Beust, Mayor and Prime Minister of the City State of Hamburg, visits BNI.

February 28th, 2004
Seminar for physicians: „Fever after sojourn in the tropics".

March 6th, 2004
7th Symposium on Dermatology and Travel Health on "Mycoses and Mycobacterioses abroad and at home". Organized in co-operation with the Society for Dermatology in the Tropics (programme on page 132).

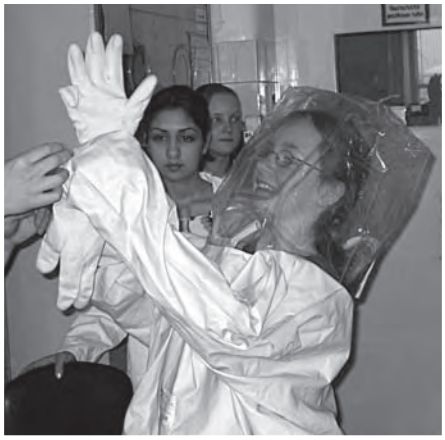
March 27th, 2004
Day of Travel Health
(organized by the Centre for Travel Advice, BNI).

April 5th – June 30th, 2004
Course on Tropical Medicine (see also page 114/115).

April 7th, 2004
Jürgen Klimke, Member of Parliament, pays a visit to BNI.

April 13th, 2004
Jörg Dräger, PhD, Minister of Science and Health of the City State of Hamburg, pays a visit to BNI.

April 29th, 2004
Girls' Day



„Handgreifliche" Berufserkundung: Acht Mädchen im Alter von 11-17 Jahren schlüpften am Girls Day 2004 in die Rolle von Ärztinnen und klärten einen Fall von tropischem Fieber auf. Foto: M. Adler, BNI.

Hands-on professional experience: Eight girls aged 11-17 act as future physicians and investigate a case of fever after sojourn in the tropics. Photo: M. Adler, BNI.

10. Mai 2004
Informationsbesuch der Wissenschafts- und Kulturreferenten ausländischer Botschaften.

Lernten die Institute der Leibniz-Gemeinschaft kennen: Wissenschafts- und Kulturreferenten der ausländischen Botschaften in Deutschland.
Foto: K. Jürries, BNI.

May 10th, 2004
Executives of the embassies in Germany pay an information visit to the institute.

Getting to know institutes of the Leibniz Association: Executives of the embassies in Germany.
Photo: K. Jürries, BNI.

27. Mai 2004
„Globale Infektionen – was kommt nach SARS?“ Informationsveranstaltung in Zusammenarbeit mit der Handelskammer Hamburg

May 27th, 2004
“Global infections – SARS revisited”. Information evening in the Hamburg Chamber of Commerce.

15. Juni 2004
After School Talk: „Forschen und Arbeiten in den Tropen“. Veranstaltung im Rahmen des Projekts „Mehr Jugend in die Wissenschaft!“

June 15th, 2004
After School Talk: “Working and living as a guest scientist in Ghana”. Seminar event in the BNI young scientist programme.

16. Juni 2004
Mitgliederversammlung der Vereinigung der Freunde des Tropeninstituts Hamburg e.V.
Dr. rer. nat. Zita Krnajski (Abteilung für Biochemie) erhält den Doktorandenpreis 2004 für die Dissertation mit dem Titel: „Das Thioredoxin Redox-System von *Plasmodium falciparum*“.

Doktorandenpreisträgerin Dr. Zita Krnajski.
Foto: privat.

June 16th, 2004
Annual meeting of the sponsoring association “*Vereinigung der Freunde des Tropeninstituts Hamburg e.V.*“. The association´s annual best thesis award went to Dr. rer. nat. Zita Krnajski (Department of Biochemistry) for her thesis „Thioredoxin redox system of *Plasmodium falciparum*“.

Best thesis award: Dr. Zita Krnajski.
Photo: private.

18./19. Juni 2004
5. Arbeitstreffen des EU-Konsortiums „Pregnancy-associated Malaria vaccine“ (Organisation: Mo Klinkert).

June 18th/19th, 2004
5th PAMVAC Project Meeting „Pregnancy-associated Malaria vaccine“ (funded by the European Commission). Organization: Mo Klinkert.

25. Juni 2004
„Berufswege von Frauen in der Biomedizin“, Forum für Schülerinnen und Studentinnen im Rahmen des Projekts „Mehr Jugend in die Wissenschaft!“

June 25th, 2005
“Women´s careers in biomedical sciences”. Forum for women in the BNI young scientist programme.

23. Juni 2004
Seminarexkursion Tropenmedizin
für Studierende der Medizin (ganztägig).

28. Juni 2004
Informationsbesuch der AG Tourismus der CDU/CSU Bundestagsfraktion.

27. Oktober 2004
Delegation aus dem Gesundheitswesen Shanghai zu Gast im BNI.

29. Oktober 2004
7. Reisemedizinisches Update in Zusammenarbeit mit Aventis Pasteur MSD.

18. – 22. Oktober 2004
„Medizin in den Tropen“, Kurs für medizinisches Fachpersonal.

June 23rd, 2004
Day seminar on tropical medicine for university students.

June 28th, 2004
The CDU/CSU parliamentary party´s working group on tourism pays a visit to BNI.

October 27th, 2004
A delegation from the Shanghai Health Services pays a visit to BNI.

October 29th, 2004
7th Travel Medicine Update in co-operation with Aventis Pasteur MSD.

October 18th – 22th, 2004
“Practising medicine in the tropics”, course for medical professionals.

July 2004: Two sights on the river Elbe – Queen Mary 2 and BNI.
Juli 2004: Zwei Sehenswürdigkeiten am Hamburger Hafen – die Queen Mary 2 und das BNI.

2005

20./21. Januar 2005
Sitzung des Wissenschaftlichen Beirats.

02. Februar 2005
Startschuss für Erweiterungsbau:
Abriss des Tierhauses.

Blick aus dem Hörsaal auf das Tierhausgelände: Nach Abriss des alten Tierhauses entsteht hier der Erweiterungsbau.
Foto: K. Jürries, BNI.

Development of the building site: the old animal house gives way to a modern laboratory building.
Photo: K. Jürries, BNI.

12. Februar 2005
Tag der Reisegesundheit
(Organisation: Reisemedizinisches Zentrum).

14. Februar 2005
Dr. Kurt Eckernkamp, Verleger und Aufsichtsratsvorsitzender der Vogel Medien Gruppe Würzburg, würdigt die Arbeit des BNI im Rahmen der Feierlichkeiten zu seinem 70. Geburtstag mit einer Spende der Vogel Stiftung in Höhe von 30.000 Euro.

1. Leibniz-Forum in der Handelskammer Hamburg mit 240 Teilnehmern. Thema:
„Tuberkulose, Aids, SARS – die neuen Plagen".
Grußworte: Hans-Olaf Henkel (Präsident der Leibniz-Gemeinschaft) und Jörg Dräger, PhD (Senator für Wissenschaft und Gesundheit).

04. April – 30. Juni 2005
Diplomkursus Tropenmedizin (s. auch Seite 116/117).

28. April 2005
Girls' Day im Tropeninstitut: 50 Teilnehmerinnen informieren sich über die Arbeit der Virologin Petra Emmerich.

28./29. April 2005
6th Drug Development Seminar: Antiparasitic Chemotherapy (Programm s. Seite 133/134).

January 20th/21st, 2005
Meeting of the Scientific Advisory Board.

February 2nd, 2005
Construction works for the BNI laboratory extension start with the demolition of the old animal house.

February 12th, 2005
Day of Travel Health (organized by the Centre for Travel Advice, BNI).

February 14th, 2005
On occasion of his 70th birthday Dr. Kurt Eckernkamp, executive chairman of the Würzburg-based Vogel Media Group, donates 30.000 Euro of the Vogel Stiftung to BNI in appreciation of its work as a reference centre for tropical diseases.

Leibniz Forum in the Hamburg Chamber of Commerce: An audience of 240 citizens participates in the public discussion on "Tuberculosis, AIDS, SARS – the new plagues". Addresses by Hans-Olaf Henkel (President of the Leibniz Association) and Jörg Dräger, PhD (Senator for Science and Health, Hamburg).

April 4th – June 20th, 2005
Course on Tropical Medicine (see also page 114/115).

April 28th, 2005
Girls' Day: 50 future scientists learn about the work of virologist Petra Emmerich.

April 28th/29th, 2005
6th Drug Development Seminar: Antiparasitic Chemotherapy (Programme on page 133/134).

06. Juni 2005

Mitgliederversammlung der Vereinigung der Freunde des Tropeninstituts Hamburg e.V. Dr. med. Thorsten Thye erhält den Doktorandenpreis 2005 für die Dissertation mit dem Titel „Genomweite Kopplungsanalyse zur Identifizierung chromosomaler Regionen mit Einfluss auf die *Helicobacter pylori* Infektion“.

Doktorandenpreisträger Dr. Thorsten Thye (Abteilung für tropenmedizinische Grundlagenforschung). Foto: K. Jürries, BNI.

June 6th, 2005

Annual meeting of the sponsoring association “*Vereinigung der Freunde des Tropeninstituts Hamburg e.V.*“. The association´s annual best thesis award went to Dr. med. Thorsten Thye for his thesis „Using genome wide linkage analysis to identify chromosomal regions influencing *Helicobacter pylori* infection“.

Best thesis award: Dr. Thorsten Thye (Department of Molecular Medicine). Photo: K. Jürries, BNI.

08. – 12. Juni 2005

8. Kongress für Infektionskrankheiten und Tropenmedizin, Congress Centrum Hamburg (CCH).

June 8th – 12th, 2005

8th Congress on Infectious Diseases and Tropical Medicine, Congress Centre Hamburg.

11. Juni 2005

Verleihung der Bernhard-Nocht-Medaille an Prof. Dr. Vincent Deubel, Direktor des Institut Pasteur in Shanghai, für seine Verdienste um die Tropenvirologie.

June 12th, 2005

Award of the Bernhard Nocht Medal to Prof. Vincent Deubel, Director the Institute Pasteur Shanghai, for his contributions to tropical virology.

Die Bernhard-Nocht-Medaille wird vom BNI gemeinsam mit der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit verliehen und von der Vereinigung der Freunde des Tropeninstituts Hamburg e.V. gestiftet. Links Prof. Vincent Deubel, rechts Prof. Bernhard Fleischer, Direktor des BNI. Foto: K. Jürries, BNI.

The Bernhard Nocht Medal is awarded by BNI and the German Society for Tropical Medicine and International Health and endowed by the sponsoring association “*Vereinigung der Freunde des Tropeninstituts Hamburg e.V.*“. Prof. Vincent Deubel (left) and Prof. Bernherd Fleischer, Director of BNI. Photo: K. Jürries, BNI.

28. Juni 2005

Großes Instituts-Sportfest mit 80 Aktiven: Mannschaften von BNI, Tropenkurs und Artus Biotech GmbH messen sich in den Disziplinen Fußball, Beach-Volleyball und Tennis.

June 28th, 2005

Sports meeting of BNI, Tropical Medicine Course and ArtusBiotech GmbH. 80 athletes compete in football, beach volleyball and tennis.

12. Juli 2005
Grundsteinlegung für den Erweiterungsbau (s. auch Seite 174/175). Grußworte: Bundesgesundheitsministerin Ulla Schmidt, Erster Bürgermeister Ole von Beust, Architektin Prof. Susanne Gross (Büro Kister Scheithauer Gross, Köln).

25. Juli 2005
Informationsveranstaltung für Führungskräfte aus dem Gesundheitswesen in Bosnien-Herzegowina (in Zusammenarbeit mit der Behörde für Wissenschaft und Gesundheit).

19. August 2005
Bundeswehr und Bernhard-Nocht-Institut unterzeichnen Vertrag über Zusammenarbeit in der ambulanten und klinischen Tropenmedizin.

21. September 2005
Besuch des Botschafters von Madagaskar Dr. Denis Andriamandroso in Begleitung von Honorargeneralkonsul Eckhard Koll, Jörg Grigoleit (Geschäftsführer Havelland Kliniken GmbH) sowie Prof. Dr. Jens Brümmer (Universitätsklinikum Hamburg-Eppendorf).

17. – 28.Oktober 2005
Kurs „Medizin in den Tropen“ für medizinisches Fachpersonal.

18. Oktober 2005
Leibniz-Forum im Hanse-Office Brüssel: „The old new plagues – AIDS, SARS, TB“.

July 12th, 2005
Laying of cornerstone ceremony for the BNI extension building (see page 174/175). Addresses by Ulla Schmidt (Federal Ministry of Health), Ole von Beust (Mayor and Prime Minister of the City State of Hamburg), Prof. Susanne Gross (architect of Kister Scheithauer Gross, Cologne).

July 25th, 2005
Public Health Administrators from Bosnia Herzegowina pay a visit to the BNI (in co-operation with the Hamburg Ministry of Science and Health).

August 18th, 2005
BNI and Federal Armed Forces sign a contract on co-operation in tropical medicine patient care.

September 21st, 2005
Dr. Denis Andriamandroso, Ambassador of Madagaskar, Honorary Consul General Eckard Kroll, Jörg Grigoleit (Managing Director Havelland Kliniken GmbH) and Prof. Dr. Jens Brümmer (University Medical Centre Hamburg-Eppendorf) pay a visit to BNI.

October 17th – 28th, 2005
“Practising medicine in the tropics”, course for medical professionals.

October 18th, 2005
Leibniz Forum at the Hanse Office, Brussels: „The old new plagues – AIDS, SARS, TB“.

Experten auf dem Leibniz-Forum. Von links nach rechts: Prof. Dr. Joachim Hauber (Heinrich-Pette-Institut, Hamburg), Dr. Hellmut Körner (Ministerium für Soziales und Gesundheit, Schleswig-Holstein), Dr. Peet Tüll (European Centre for Disease Prevention and Control), Prof. Dr. Bernhard Fleischer (BNI), Dr. Sabine Rüsch-Gerdes (Forschungszentrum Borstel), Abigail Wright (Stop TB Department, WHO). Foto: Leibniz-Gemeinschaft.

Experts at the Leibniz Forum. From left to right: Prof. Dr. Joachim Hauber (Heinrich Pette Institute, Hamburg), Dr. Hellmut Körner (Ministry of Social Affairs and Health, Schleswig-Holstein), Dr. Peet Tüll (European Centre for Disease Prevention and Control), Prof. Dr. Bernhard Fleischer (BNI), Dr. Sabine Rüsch-Gerdes (Research Centre Borstel), Abigail Wright (Stop TB Department, WHO). Photo: Leibniz-Gemeinschaft.

20. Oktober 2005
Besuch des stellvertretenden Bürgermeisters von Taipeh, Yeh Chin-chuan.

31.Oktober – 04. November 2005
1. Aufbaukurs für medizinisches Fachpersonal – Malaria und andere Blutparasitosen.

21. Oktober 2005
„Clinical Virology and Emerging Pathogens“ Abschiedssymposium für Prof. Dr. Herbert Schmitz, Leiter der Abteilung für Virologie (Programm s. Seite 135).

28./29. Oktober 2005
2. Malaria-Treffen der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. und der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit (Programm s. Seite 136/137).

29./30. Oktober 2005
Experten-Workshop Malaria des Forum Reisen und Medizin e.V.

October 20th, 2005
Deputy Mayor Yeh Chin-chuan of Taipei pays a visit to BNI.

October 31st – November 4th, 2005
“Malaria and other blood parasitoses”, course for medical professionals.

October 21st, 2005
„Clinical Virology and Emerging Pathogens“, symposium on occasion of the 65th birthday of Prof. Dr. Herbert Schmitz, Head Department of Virology (programme see page 135).

October 28th/29th, 2005
2nd Malaria Meeting of the Paul Ehrlich Society for Chemotherapy and the German Society for Tropical Medicine and International Health (programme see page 136/137).

October 29th/30th, 2005
Expert workshop Malaria of the Forum for Travel and Medicine.

29. Oktober 2005
1. Nacht des Wissens in Hamburg (gefördert von der Nordmetall-Stiftung): 2000 Besucher erleben einen Blick hinter die Kulissen des Tropeninstituts (s. auch Seite 104/105).

October 29th, 2005
1st Night of Science in Hamburg (sponsored by the Nordmetall Foundation): 2000 citizens visit BNI and explore the extensive scientific activities organised by more than fifty BNI volunteers.

1. November 2005
Das Universitätsklinikum Hamburg-Eppendorf (UKE) übernimmt die Klinische Abteilung des Bernhard-Nocht-Instituts. BNI und UKE unterzeichnen einen Vertrag zur klinisch-wissenschaftlichen Kooperation.

7. November 2005
Vorlesung von Prof. Fleischer vor 800 kleinen Zuhörern an der Kinderuni Hamburg: „Wozu braucht man Impfungen?“

18. – 20. November 2005
2. Refresher Kurs Tropenmedizin (organisiert von der Klinischen Abteilung).

November 1st, 2005
The University Medical Centre Hamburg-Eppendorf (UKE) takes over management of the BNI Clinical Department. The parties sign a contract for clinical and scientific co-operation.

November 7th, 2005
800 young listeners at the children´s university Hamburg attend a talk of Prof. Fleischer on the importance of immunizations.

November 18th – 20th, 2005
2nd Refresher Course on Tropical Medicine (organized by the Clinical Department).

01./02. Dezember 2005
Sitzung des wissenschaftlichen Beirates.
Die bisherigen Vorsitzenden Prof. Dr. Jürgen Heesemann (München) und Prof. Dr. Philippe Sansonnetti (Paris) werden verabschiedet. Zur neuen Vorsitzenden wird Frau Prof. Dr. Ulrike Beisiegel (Hamburg) gewählt. Stellvertreter ist Prof. Dr. Rudi Balling (Braunschweig).

8. Dezember 2005
Die Bürgerschaft der Freien und Hansestadt Hamburg stimmt dem Verkauf und der Übertragung der Klinischen Abteilung an das Universitätsklinikum Hamburg-Eppendorf zu (Drucksache 18/3051).

19. Dezember 2005
Bundesgesundheitsministerin Ulla Schmidt verleiht vier Wissenschaftlern des BNI den Bundesverdienstorden.

December 1st/2nd, 2005
Meeting of the Scientific Advisory Board. The terms of office of chairman Prof. Dr. Jürgen Heesemann (Munich) and vice chairman Prof. Dr. Philippe Sansonnetti (Paris) end. Prof. Dr. Ulrike Beisiegel (Hamburg) and Prof. Dr. Rudi Balling (Braunschweig) are elected as chairwoman and vice chairman.

December 8th, 2005
The Hamburg state parliament decides on the transfer of the Clinical Department to the University Medical Centre Hamburg-Eppendorf.

December 19th, 2005
Four scientists of BNI receive the Bundesverdienstorden, Germany´s highest national decoration.

Die Pathologen Prof. Dr. Paul Racz und Dr. Klara Tenner-Racz erhalten die Auszeichnung von Ministerin Schmidt (Mitte) für ihr wissenschaftliches Lebenswerk. Foto: BMG.

Pathologists Prof. Dr. Paul Racz and Dr. Klara Tenner-Racz are honoured for their contributions to HIV research. Middle: Ulla Schmidt, Federal Minister of Health, who awarded the decoration.
Photo: BMG.

Die Virologen Dr. Stephan Günther und Dr. Christian Drosten wurden für die Identifizierung des SARS-Coronavirus mit dem Bundesverdienstorden geehrt. Foto: K. Jürries, BNI.

Virologists Dr. Stephan Günther and Dr. Christian Drosten receive the decoration for the identification of SARS coronavirus in 2003.
Photo: Klaus Jürries, BNI.

21. Dezember 2005
Feier für die Träger der Bundesverdienstorden im Hamburger Rathaus. Laudatio: Jörg Dräger, PhD (Senator für Wissenschaft und Gesundheit).

December 21st, 2005
The Senator of the Hamburg Ministry of Science and Health gives a reception at the Town Hall for the decorated scientists.

Some colleagues prefer to stay at street level.
Zaungäste: Einige Kollegen bevorzugen die Straßenhöhe.

June 12th, 2005
LAYING OF CORNERSTONE
for the BNI
extension building

Others dare to descent into the excavation pit.
Andere wagen den Abstieg in die Baugrube.

A hot summer day on the construction site. In 2007 this site will harbour a modern research infrastructure with specific-pathogen free animal husbandry, an insectary and biological safety laboratories up to level 4.
Ein heißer Sommertag auf dem Baugelände. An dieser Stelle wird bis 2007 ein Gebäude mit modernen Tierställen, einem Insektarium und Hochsicherheitslaboratorien entstehen.

12. Juni 2005
GRUNDSTEINLEGUNG
für den
Erweiterungsbau

A moment of contemplation.
Ein Moment der Ruhe.

The cornerstone, a concrete box, traditionally is filled with documents and sealed. From left to right: Ole von Beust (Mayor and Prime Minister of Hamburg), Dietrich Wersich (State Secretary in the Hamburg Ministry of Science and Health) and Ulla Schmidt (Federal Minister of Health). Bernhard Fleischer, Director of BNI, keeps in the background.
Der Grundstein enthält einen Hohlraum, der traditionell mit Dokumenten und eine Tageszeitung gefüllt und versiegelt wird.
Von links nach rechts: Erster Bürgermeister Ole von Beust, Staatsrat Dietrich Wersich (Behörde für Wissenschaft und Gesundheit), Bundesgesundheitsministerin Ulla Schmidt. Im Hintergrund: Institutsdirektor Bernhard Fleischer.

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