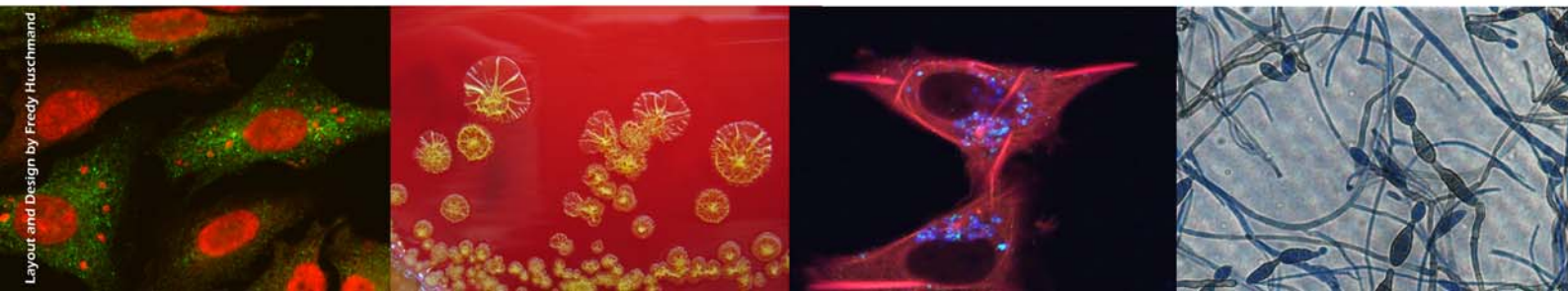
Studyguide for the Major ‚Infectious Diseases'

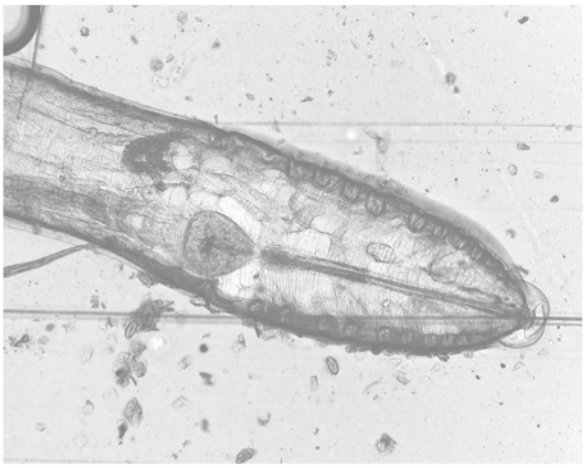
for Students of Bachelor Study Courses in 'Biology' and 'Molecular Cell Biology' in the faculty of Bio Sciences

- Infectious Diseases - A Brief Description
- Education at the Institute of Hygiene
- Research at the Institute of Hygiene
- Content and Structure of the Major 'Infectious Diseases'
- Aquired Degree
- Contact Persons and Addresses
- Department Profiles

Layout and Design by Fredy Huschmand



Infectious Diseases - A Brief Description



Studies of infectious diseases at the molecular and cellular level are a rather new research area, whose origin as an independent scientific discipline can be traced back to the discovery of microorganisms. Even though infectious diseases have been known for thousands of years, exact knowledge of their source emerged only in the past century. Thus, the discovery of bacteria and viruses e.g. as cause for certain diseases began just in the middle of the 19th century.

Nowadays it is common knowledge that infectious diseases are caused by bacteria, viruses, fungi or parasites, and the rising threats from multiresistant bacteria or the emergence of new pathogens like influenza or SARS are frequently in the news. Apart from their enormous medical significance, however, microorganisms are important model systems for molecular and cell biology.

For example, RNA splicing was discovered in adenoviruses, oncogenes were found for the first time in retroviruses and the structure of nucleosomes was described primarily in DNA viruses. Today, the science of infectious diseases is an interdisciplinary topic at the interface between medicine and molecular and cell biology.

With this fact in mind, the newly created Major “Infectious Diseases” within the MSc “Molecular Biosciences” offers the opportunity to study this topic in considerable depth, both in theory and in practice.

Education at the Institute for Hygiene

The Institute for Hygiene at the Medical Faculty of Heidelberg represents the subject of Infectious Diseases in research, education and diagnostics, in the fields of bacteriology, virology, parasitology and public health. There are five departments, most of which are involved in the educational activities of this Major.

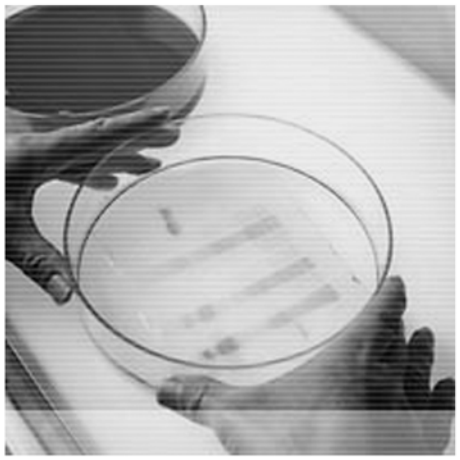
These departments are:

- Department of Medical Microbiology and Hygiene
- Department of Parasitology
- Department of Virology
- Department of Molecular Virology
- Department of Tropical Diseases and Public Health

Most department heads are members of both the Faculty of Biosciences and the medical faculty and therefore are involved in teaching in both faculties. Previous lecture series and practicals in Biosciences, which were performed partially in collaboration with study groups at the Center for Molecular Biology Heidelberg (ZMBH) and the German Cancer Research Centre (DKFZ) were always well attended and dealt with molecular- and cell-biological aspects of medically important infectious diseases and their causative agents. Thus they covered an interdisciplinary field of high relevance.

Detailed information regarding the contents of the individual lectures (e.g. collection of slides) can be found on the websites of the corresponding departments. The internet links are provided under “contact and addresses”.

Research at the Institut of Hygiene



The main research topics of the departments include HIV/Aids, malaria, viral hepatitis and the interaction between bacteria and host cells (immunology of infection). All departments are well integrated into different local and international research consortia and networks, some of which are coordinated by departments of the institute.

One example is the research network "Control of tropical infectious diseases" (Sonderforschungsbereich 544"). In addition there are close interactions and scientific cooperations with numerous institutions of Heidelberg University, the European Laboratory for Molecular Biology (EMBL), the German Cancer Research Center (DKFZ) and the Max-Planck-Institute for Medical Research. In addition, we collaborate with numerous institutions in Europe and beyond.

To find out more about the scientific research activities of the Institute for Hygiene, the ZMBH-group and the associated research groups participating in this Major, please look at the profiles, which are in the appendix and the corresponding websites.

The Institute for Hygiene aims to further extend and strengthen these research activities in particular by integrating interdisciplinary approaches and most recent technologies. These include high-resolution light and electron microscopy with the three-dimensional reconstruction of complex cellular structures, high through-put method screening for proteome and transcription analyses as well as time-resolved analysis of pathogen / host-cell interactions by using live cell imaging, mathematic modelling and simulation.

Content and Structure of the Major 'Infectious Diseases'

Content

The Major 'Infectious Diseases' is intended for students with a good basic knowledge of molecular and cell biology who wish to put their main focus on infectious disease pathogens. In the context of the Major they will deepen their knowledge of the basics of molecular and cell biology and get to know specific aspects of the replication of infectious pathogens and their interactions with their hosts. The participating departments and research groups offer internationally renowned research programs as well as an excellent infrastructure and they are very well connected with other research institutions inside and outside the university. Therefore, they offer ideal conditions for the Major "Infectious Diseases".

Criteria for admission

We welcome appropriately qualified students from all over the world to this course. Modern infectious disease research focuses on molecular mechanisms of pathogenesis, so a good basic knowledge of molecular and cell biology is a prerequisite for admission. Some prior knowledge of infectious disease biology and immunology is also helpful, but not a prerequisite.

Aquired Degree

With the successful completion of the course the student acquires the MSc in Biology with the specialization (Major) "Infectious Diseases". This Masters degree qualifies students to enter PhD programmes in Europe or could be a starting point for a career in the pharmaceutical industry or a biotech company.

Various doctoral study programmes are offered by the institutes involved in the "Infectious Diseases" Major. Further information is to be found on the websites of the participating departments. Students who are particularly keen to pursue a doctoral degree, and who have sufficiently high grades, may transfer to a doctoral programme already after 3 semesters of Masters studies.

Contact Persons and Adresses

Coordination:

INF 345, 1st Floor, Phone: +49 6221 56 4225; Fax: +49 6221 56 4570

Department Medical Microbiology and Hygiene:

Contact: Prof. Dr. Alexander Dalpke,

INF 324, 1st Floor; Phone: +49 6221 56 38173, Fax: +49 6221 56 5857;

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Consultations hours by arrangement

Internet: http://www.klinikum.uni-heidelberg.de/index.php?id=1216

Department Parasitology:

Supervisor: Prof. Dr. Michael Lanzer,

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Department Virology:

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Consultations hours by arrangement

Internet: http://www.klinikum.uni-heidelberg.de/Kontakt.4716.0.html

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Department Molecular Virology:

Supervisor: Prof. Dr. Ralf Bartenschlager,

INF 345, 1st Floor; Phone: +49 6221 56 4569; Fax: +49 6221 56 4570;

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Center for Molecular Biology (ZMBH):

Supervisor: Prof. Christine Clayton,

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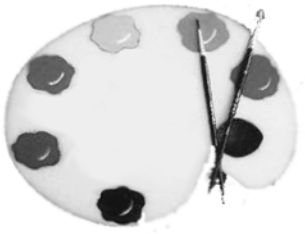
Department Profiles (Index)



Department Profiles

Medical Microbiology and Hygiene

Supervisor: Prof. Dr. Klaus Heeg
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Scientific Vita

- 1992-98 Medical student, University Göttingen
- 1998 Graduation (MD), Med. Microbiology, Center of Hygiene and Human Genetics, Med. Faculty, University Göttingen
- 1998-99 First-year resident, internal medicine (Alfeld)
- 1999-2004 Post-doc and Research Assistant, Inst. of Medical Microbiology, University Marburg
- 2004 Habilitation, university lecturer for infection and immunity, University Marburg
- 2005 Full professor for Medical Microbiology and Immunology of Infections, University Heidelberg

Fields of Interest

The focus of our research is the field of infection and immunity. We are studying the interactions between microbial compounds which are now termed PAMPs (pathogen associated microbial patterns) and cells of the innate and adaptive immune system. PAMPs are sensed by pattern recognition receptors and among these Toll-like receptors play an outstanding role. Indeed, the recent identification of Toll-like receptors has now pushed the field of innate immunity enormously and has shifted this field back into the focus of microbiologists and immunologists.

Getting more insight into the interplay of pathogens and hosts will impact our understanding of emerging problems within modern microbiology which comprise sepsis, opportunistic infections in immunocompromised patients as well as spread of multi-resistant microbes.

Groups in the department are working on:
CpG-DNA and TLR9, RNA-mediated immunostimulation, Molecular diagnostic/ pyrosequencing, Suppressor of Cytokine Signaling proteins (SOCS), Immune functions of airway epithelium, Regulation of IL-12p40, Microbial Pattern Recognition by Human B Cells, Staphylococcus aureus-induced Production of Type I Interferon, Differentiation of Dendritic Cells

Publications (10 selected publications since 2000):

1. Dalpke A, Opper S, Zimmermann S, Heeg K (2001): Suppressors of cytokine signaling (SOCS)-1 and –3 are induced by CpG-DNA and modulate cytokine responses in antigen presenting cells. J. Immunol 166:7082-7089

2. Biedermann T, Zimmermann S, Himmelrich H, Gumy A, Egeter O, Sakrauski AK, Seegmuller I, Voigt H, Launois P, Levine AD, Wagner H, Heeg K, Louis JA, Rocken M (2001): IL-4 instructs TH1 responses and resistance to Leishmania major in susceptible BALB/c mice. Nat Immunol. 2(11):1054-60.

3. Dalpke A, Eckerle S, Frey M, Heeg K (2003): Triggering of Toll-like receptors modulates IFN-? signaling: Involvement of S727-Stat-1 phosphorylation and suppressors of cytokine signaling (SOCS). Eur. J. Immunol, 33(7):1776-1787

4. Narayanan S, Dalpke AH, Siegmund K, Heeg K, and Richert C (2003): CpG Oligonucleotides with Modified Termini and Nicked Dumbbell Structure Show Enhanced Immunostimulatory Activity. J Med Chem 46(23):5031-5044

5. Albrecht I, Tapmeier T, Zimmermann S, Frey M, Heeg K, and Dalpke AH (2004): Toll-like receptors differentially induce nucleosome remodeling at the IL-12p40 promoter. EMBO Reports 5 (2), 172-177

6. Hanley PJ, Musset B, Renigunta V, Limberg SH, Dalpke AH, Sus R, Heeg KM, Preisig-Müller R, and Daut J (2004): Extracellular ATP induces oscillations in intracellular Ca2+ and membrane potential and promotes transcription of IL-6 in macrophages. PNAS 101 (25), 9479-9484

7. Platz J, Beisswenger C, Dalpke A, Koczulla R, Pinkenburg O, Vogelmeier C, and Bals R (2004): Microbial DNA induces a host defense reaction of human respiratory epithelial cells. J. Immunol. 173(2), 1219-1223

8. Bätz A, Frey M, Heeg K and Dalpke AH (2004): Suppressor of cytokine signaling (SOCS) proteins indirectly regulate Toll-like receptor signaling in innate immune cells. J. Biol. Chem. 279(52), 54708-54715

9. Bekeredjian-Ding IB, Wagner M, Hornung V, Giese T, Schnurr M, Endres S, Hartmann G (2005): Plasmacytoid dendritic cells control TLR7 sensitivity of naive B cells via type I IFN. J. Immunol. 174(7):4043-50.

10. Zimmermann S, Murray PJ, Heeg K, Dalpke AH (2006): Induction of Suppressor of Cytokine Signaling-1 (SOCS-1) by Toxoplasma gondii Contributes to Immune Evasion in Macrophages by Blocking IFN-??Signaling. J. Immunol. 176(3): 1840-1847

Department Profiles

Parasitology

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Prof. Dr. Michael Lanzer
09/13/1959, Düsseldorf

Scientific Vita

- 1984-85 Undergraduate Student, Central Research Unit, Hoffman LaRoche AG, Basel
- 1985-88 Graduate Student, Center for Molecular Biology, University of Heidelberg
- 1988-93 PostDoc, Laboratory of Biochemical Genetics, Sloan-Kettering Institute, New York
- 1994-98 Junior Group Leader, Research Center for Infectious Diseases, University of Würzburg
- 1996 Habilitation in Microbiology (Teaching and Lecturing Qualification), University of Würzburg
- 1999 - present Full Professor and Department Chair for Parasitology, University of Heidelberg
- 2000 Chair in Parasitology offered by the Seattle Biomedical Institute, USA (declined)

Parasitology

Fields of Interest

Malaria has remained one of the most important infectious diseases worldwide, causing an estimated 515 Million clinical cases and killing 1-3 Million people every year. Hopes of malaria control have been thwarted by widespread drug resistances. Malaria is caused by protozoan parasites of the genus Plasmodium, of which Plasmodium falciparum is the most virulent form. Infection starts with the bite of an infected Anopheles mosquito that transmits infective stages termed sporozoites into the human body. Sporozoites are carried with the blood flow to the liver where they invade hepatocytes. After completing their development within the liver, the parasite is released and now invades erythrocytes. Intra-erythrocytic development of the parasite is responsible for the clinical manifestation of the disease, including intermittent fever, shaking chills, organ dysfunction and the syndromes associated with cerebral and maternal malaria. Severe complications result from the ability of infected erythrocytes to adhere to the endothelial lining of venular capillaries and to sequester in the deep vascular bed.

Our laboratory focuses on drug resistance mechanisms and on the processes responsible for cytoadhesion of infected erythrocytes. In the pursuit of our research goals we use a broad range of molecular, cell biological and physiological techniques. We clone and identify putative drug transporters and study their function using heterologous systems including Xenopus laevis oocytes. Using sophisticated microscopic techniques, we investigate drug distribution within cells in order to better understand the mode of action and the basis of resistance. In collaboration with industrial partners, we try to develop novel antimalarial drugs that inhibit or circumvent drug resistance mechanisms. Other work conducted in the laboratory relates to protein trafficking from the parasite across the erythrocyte cytoplasm to the erythrocyte plasma membrane. Here we use GFP-tagged chimeric proteins in combination with confocal and electron microscopy to identify protein trafficking signals and the trafficking machinery that recognizes with these signals.

Publications (10 selected publications since 2000):

1. del Portillo, H.A., Fernandez-Becerra, C., Bowman, S., Oliver, K., Preuss, M., Sanchez, C.P., Schneider, N.K., Villalobos, J.M., Rajandream, M.A., Harris, D., Pereira da Silva, L.H., Barrell, B. and Lanzer. M. (2001) A superfamily of variant genes encoded in the subtelomeric region of Plasmodium vivax. Nature 410, 839-842.

2. Wissing, F., Sanchez, C.P., Rohrbach, P., Ricken, S. and Lanzer, M. (2002) Illumination of the malaria parasite Plasmodium falciparum alters intracellular pH. Implications for live cell imaging. J. Biol. Chem., 277, 37747-37755.

3. Andrews, K.T., Pirrit, L.A., Przyborski, J.M., Sanchez, C.P., Sterkers, Y., Ricken, S., Wickert, H., Lepolard, C., Avril, M., Scherf, A., Gysin, J. and Lanzer, M. (2003) Recovery of adhesion to chondroitin-4-sulphate in Plasmodium falciparum varCSA disruption mutants by antigenically similar PfEMP1 variants. Mol. Microbiol., 49, 655-669.

4. Sanchez, C.P., Stein, W. and Lanzer, M. (2003) Trans stimulation provides evidence for a drug efflux carrier as the mechanism of chloroquine resistance in Plasmodium falciparum. Biochemistry, 42, 9383-9394.

5. Sanchez, C., McLean, J.E., Stein, W. and Lanzer, M. (2004) Evidence for a substrate specific and inhibitable drug efflux system in chloroquine resistant Plasmodium falciparum strains. Biochemistry, 43, 16365-16373.

6. Nessler, S., Friedrich, O., Bakouh, N., Fink, R.H., Sanchez, C.P., Planelles, G. and Lanzer, M. (2004) Evidence for activation of endogenous transporters in Xenopus laevis oocytes expressing the Plasmodium falciparum chloroquine resistance transporter, PfCRT. J. Biol. Chem., 279, 39438-39446.

7. Wickert, H., Gottler, W., Krohne, G. and Lanzer M. (2004) Maurer's cleft organization in the cytoplasm of Plasmodium falciparum-infected erythrocytes: new insights from three-dimensional reconstruction of serial ultrathin sections Eur. J. Cell Biol., 83, 567-582.

8. Rohrbach, P., Friedrich, O., Hentschel, J., Plattner, H., Fink, R.H. and Lanzer M. (2005) Quantitative calcium measurements in subcellular compartments of Plasmodium falciparum-infected erythrocytes. J. Biol. Chem., 280, 27960-27969.

9. Przyborski, J.M. Miller, S.K., Pfahler, J.M., Rohrbach, P., Crabb, B.S. and Lanzer, M. (2005) Trafficking of STEVOR to the Maurer's clefts in P. falciparum infected erythrocytes. EMBO J., 24, 2306-2317.

10. Sanchez, C.P., McLean, J.E., Rohrbach, P., Fidock, D.A., Stein, W.D. and Lanzer, M. (2005) Evidence for a pfcrt-associated chloroquine efflux system in the human malarial parasite Plasmodium falciparum. Biochemistry, 44, 9862-9870.

Department Profiles

Virology

Supervisor/Contact Person : Prof. Dr. Hans-Georg Kräusslich

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01/11/1959, Passau

Scientific Vita

- 1977 - 1984 Medical School (Munich)
- 1985 MD in experimental virology (Munich)
- 1986 - 1989 PostDoc, Dept. of Molecular Biology, State Univ. New York at Stony Brook
- 1989 - 1993 Group leader, German Cancer Research Centre, Heidelberg
- 1990 Habilitation, University of Heidelberg
- 1993 - 1995 Head of junior department, German Cancer Research Centre, Heidelberg
- 1995 - 1999 Full professor and head of department, Heinrich-Pette-Institute, Hamburg
- 1996 - 1999 Director, Heinrich-Pette-Institute, Hamburg
- 2000 – now Full professor and head of department for virology, University of Heidelberg
- 2004 – now Director Hygiene-Institute, University Heidelberg
- 2004 – now Coordinator research program 'Infectious diseases', University Heidelberg

Fields of Interest

The main focus of research in the department of virology is on human immunodeficiency virus (HIV), the causative agent of AIDS. With more than 40 million people infected and 5 million new infections and 3 million deaths per year, AIDS continues to be one of the most important health threats of our time. Most of the research projects in the department address the molecular and structural biology of the virus and its interaction with the host cell. In addition, we perform clinically oriented research projects on prevention of mother to child transmission of HIV and regarding development and diagnosis of resistance against antiviral drugs.

The main focus of basic research projects in the department is on the assembly, structure and entry of HIV in tissue culture and in in vitro systems. Besides viral functions, we are also studying the involvement and role of host cell factors in these processes. Additional topics concern viral regulatory proteins and in particular the pathogenesis factor Nef as well as the development of transgenic small animal models for HIV infection and AIDS. The research questions are addressed by a combination of biochemistry and molecular cell biology techniques with strong collaborations in structural biology, in particular relating to high resolution cryo electron microscopy and tomography. We have also developed unique fluorescent viral systems for live cell video microscopy of HIV infection and quantitative analysis of diverse stages of the replication paths. Using these systems we aim at a quantitative and time resolved description of the viral entry process, eventually leading to mathematical models of entry. A main aspect of all research projects concerns the evaluation and exploitation of novel targets for antiviral therapy, which is of utmost importance for future control of the AIDS pandemic.

Publications *(10 selected publications since 2000):*

1. Brügger, B., B. Glass, P. Haberkant, I. Leibrecht, F.T. Wieland and H.-G. Kräusslich. 2006. The HIV lipidome: A raft with an unusual composition. Proc. Natl. Acad. Sci. USA 103: 2641-2646.

2. Briggs, J.A.G., K. Grünewald, B. Glass, F. Förster, H.-G. Kräusslich and S. Fuller. 2006. The mechanism of HIV-1 core assembly: insights from three-dimensional reconstructions of authentic virions. Structure 14: 15-20.

3. Ternois F., J. Sticht, S. Duquerroy, H.-G. Kräusslich and F. A. Rey. 2005. Crystal structure of the HIV-1 capsid protein C-terminal domain in complex with an inhibitor of particle assembly. Nat. Struct. Mol. Biol. 12: 678-682.

4. Sticht, J., M. Humbert, S. Findlow, J. Bodem, B. Müller, U. Dietrich, J. Werner and H.-G. Kräusslich. 2005. A Peptide Inhibitor of HIV-1 Assembly in vitro. Nat. Struct. Mol. Biol. 12: 671-677.

5. Wakita, T., T. Pietschmann, T. Kato, T. Date, M. Miyamoto, Z. Zhao, K. Murthy, A. Habermann, H.-G. Kräusslich, M. Mizokami, R. Bartenschlager and T.J. Liang. 2005. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. Nat. Med. 11: 791-796.

6. Müller, B., J. Daecke, O.T. Fackler, M.T. Dittmar, H. Zentgraf and H.-G. Kräusslich. 2004. Generation of a fluorescently labelled infectious HIV-1 derivative. J. Virol. 78: 10803-10813.

7. Briggs, J.A.G., M.N. Simon, I. Gross, H.-G. Kräusslich, S.D. Fuller, V.M. Vogt and M.C. Johnson. 2004. The stoichiometry of Gag protein in HIV-1. Nat. Struct. Mol. Biol. 11: 672-675.

8. von Schwedler, U., M. Stuchell, B. Müller, D. Ward, H.-Y. Chung, E. Morita, H. E. Wang, T. Davis, G.-P. He, D. M. Cimbora, A. Scott, H.-G. Kräusslich, J. Kaplan, S. G. Morham and W. I. Sundquist. 2003. The Protein Network of HIV Budding. Cell 114: 701-713.

9. Briggs, J.A.G., T. Wilk, R. Welker, H.-G. Kräusslich and S. D. Fuller. 2003. The structural organization of authentic HIV-1 and its core. EMBO J. 22: 1707-1715.

10. Gross, I., H. Hohenberg, T. Wilk, K. Wiegers, M. Grättinger, B. Müller, S. Fuller and H.-G. Kräusslich. 2000. A conformational switch controlling HIV-1 morphogenesis. EMBO J. 19: 103-113.

Department Profiles

Molecular Virology

Supervisor/Contact Person: Prof. Dr. Ralf Bartenschlager

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Scientific Vita

- 1981-87 Studies in Biology (Heidelberg)
- 1990 PhD in Molecular Biology
- 1991 PostDoc, Center for Molecular Biology, Heidelberg
- 1992-93 PostDoc, Central Research Unit, Hoffmann-La Roche AG, Basel
- 1994-98 Assistant, University of Mainz
- 1999 Habilitation, University of Mainz
- 2001 Full professor for Molecular Biology, University of Mainz
- 2002 - now Ordinarius for Molecular Virology, University of Heidelberg

Molecular Virology

Fields of Interest

Teams in the department Molecular Virology work on several highly important human pathogens, namely hepatitis B virus (HBV), hepatitis C virus (HCV) and Dengue virus (DV). These viruses are leading causes for death worldwide with about 500 million people suffering from a chronic infection with the two hepatitis viruses and about 100 million new DV infections occurring each year especially in tropical countries.

As a department that focuses on molecular aspects of these infections the following topics are studied: virus-host cell interaction, mechanism of host cell infection, live cell imaging and electron microscopy studies of infected cells, virus assembly and involved host cell factors, RNA replication, proteases and polymerases and their utility for antiviral therapy, RNA structures and their role for viral replication, mathematical modelling and simulation of virus replication, transcriptome analysis of virus-induced host cell genes, innate immunity and viral counter measures, antiviral therapy and therapy resistance. In order to cover these topics, we are using a broad and diverse array of methods and experimental approaches covering the fields of molecular biology, cell biology, biochemistry and immunology.

Publications (10 selected publications since 2000):

1. Krieger, N., V. Lohmann and R. Bartenschlager. Enhancement of hepatitis C virus RNA replication by cell culture adaptive mutations. Journal of Virology, 75:4614-4624 (2001).

2. Friebe, P., V. Lohmann, N. Krieger and R. Bartenschlager. Sequences in the 5' non-translated region of the hepatitis C virus required for RNA replication. Journal of Virology, 75:12047-57 (2001).

3. Frese, M., V. Schwärzle, K. Barth, N. Krieger, V. Lohmann, S. Mihm, O. Haller and R. Bartenschlager. Interferon-gamma inhibits replication of subgenomic and genomic hepatitis C virus RNAs. Hepatology, 35:694-703 (2002).

4. Moradpour, D., E. Bieck, T. Hügle, W. Wels, J. Z. Wu, Z. Hong, H. E. Blum and R. Bartenschlager. Functional properties of a monoclonal antibody inhibiting the hepatitis C virus RNA-dependent RNA polymerase. Journal of Biological Chemistry, 277:593-601 (2002).

5. Pietschmann, T., V. Lohmann, A. Kaul, N. Krieger, G. Rinck, G. Rutter, D. Strand and R. Bartenschlager. Persistent and transient replication of full-length hepatitis C virus genomes in cell culture. Journal of Virology;76:4008-21 (2002).

6. Lohmann, V., S. Hoffmann, U. Herian, F. Penin, and R. Bartenschlager. Viral and cellular determinants of hepatitis C virus RNA replication in cell culture. Journal of Virology 77:3007-3019 (2003).

7. Appel, N., U. Herian, and R. Bartenschlager. Efficient rescue of hepatitis C virus RNA replication by trans-complementation with nonstructural protein 5A. Journal of Virology, 79:896-909 (2005).

8. Wakita, T.*, T. Pietschmann*, T. Kato, T. Date, M. Miyamoto, Z. Zhao, K. Murthy, A. Habermann, H.-G. Kräusslich, M. Mizokami, R. Bartenschlager*, and T.J. Liang. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. Nature Medicine, 11:905 (2005).

9. Meylan, E., J. Curran, K. Hofmann, D. Moradpour, M. Binder, R. Bartenschlager, and J. Tschopp. 2005. Cardif is a novel adaptor protein in RIG-I mediated antiviral responses targeted by hepatitis C virus. Nature, 437:1167-72.

10. Pietschmann, T., A. Kaul, G. Koutsoudakis, A. Shavinskaya, S. Kallis, E. Steinmann, K. Abid, F. Negro, M. Dreux, F.-L. Cosset and R. Bartenschlager. 2006. Construction and characterization of infectious intra- and intergenotypic Hepatitis C virus chimeras. Proc. Natl. Acad. Sci. USA, 103:7408-13.

Department Profiles

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- 1972-1975 Bachelor of Biochemistry, University of Cambridge, UK
- 1975-1978 PhD student, National institute for Medical research, Mill Hill, London, UK
- 1979 PhD (Zoology) University of London, UK
- 1978-1981 Post-doctoral Fellow, Imperial College, London, UK
- 1981-1983 Post-doctoral Fellow, Stanford University Medical Center, California, USA
- 1983-1990 Assistant Professor, The Rockefeller University, New York USA
- 1990-1990 Associate Professor, The Rockefeller University, New York USA
- 1990- now Professor for Microbiology, University of Heidelberg

Fields of Interest

African trypanosomes cause sleeping sickness in humans. The WHO estimates that about half a million people are infected, and the disease is always fatal if untreated. Since only very poor people in sub-Saharan Africa are affected, there is little pharmaceutical industry interest in the disease. The ability of the parasite to vary its surface makes vaccination an impossible goal, and the few available drugs are all extraordinarily toxic. Trypanosomes also infect cattle, horses and camels, resulting in considerable economic damage. Related parasites cause Leishmaniasis all over the tropics, and Chagas disease in South America - altogether, many millions of people are affected.

African trypanosomes are transmitted by Tsetse flies. In order to survive in both the midgut of a Tsetse fly, and the blood of a mammal, the trypanosome has to regulate expression of many genes. My research focuses on how this control of gene expression operates. Unlike other living organisms, trypanosomes and their kin do not control synthesis of RNA from the DNA at the level of transcription. Instead, all mRNAs are made. Control comes later, either by degradation of the mRNA, or by regulation of translation. We concentrate especially on the regulation of mRNA degradation, analysing both the enzymes which degrade the RNA, and the protein factors which control degradation in a sequence-specific manner. In a collaboration, we are employing quantitative methods in order to build a mathematical model of gene expression.

An additional project concerns the development of modern diagnostics for trypanosome infection. Diagnosis of East African sleeping sickness still relies exclusively on microscopy, which is very time-consuming and restricts the number of people who can be screened for the disease. We are applying modern proteomic methods to tackle this problem.

Publications (10 selected publications since 2000):

1. Clayton, C.E. (2002) Developmental regulation without transcriptional control? From fly to man and back again EMBO Journal 21, 1881-1888.

2. Helfert, S., Estévez, A., Bakker, B., Michels, P.A.M. and Clayton C.E. (2001) The roles of triosephosphate isomerase and aerobic metabolism in Trypanosoma brucei. Biochem. J. 357,117-125.

3. Estevez, A., Kempf, T. and Clayton, C.E. (2001) The exosome of Trypanosoma brucei. EMBO J. 14, 3831-3839.

4. Irmer, H. and Clayton, C.E. (2001) Degradation of the unstable EP1 mRNA in Trypanosoma brucei involves initial destruction of the 3'-untranslated region. Nucleic Acids Res. 29, 4707-4715.

5. Shahi, S., Krauth-Siegel, L. and Clayton, C.E. (2002) Overproduction of the putative thiol conjugate transporter TbMRPA causes melarsoprol resistance in Trypanosoma brucei. Mol. Microbiol. 43, 1129-1138.

6. Guerra-Giraldez, C., Quijada, L., Clayton, C.E. (2002) Compartmentation of enzymes in a microbody, the glycosome, is essential in Trypanosoma brucei. J. Cell Sci. 115, 2651.

7. Quijada, L., Guerra-Giraldez, C., Drozdz, M., Hartmann, C., Ding, M., and Clayton, C.E. (2002) Expression of the human RNA-binding protein HuR in Trypanosoma brucei induces differentiation-related changes in the abundance of developmentally-regulated mRNAs. Nucleic Acids Res. 30, 4414-4424.

8. Estévez, A.M., Lehner, B., Sanderson, C.M., Ruppert, T. and Clayton, C. (2003) The roles of inter-subunit interactions in exosome stability. J. Biol. Chem. 278, 34943-34951.

9. Voncken, F., van Hellemond, J.J., Pfisterer, I., Maier, A., Hillmer, S. and Clayton, C. (2003) Depletion of GIM5 causes cellular fragility, a decreased glycosome number and reduced levels of ether-linked phospholipids in trypanosomes. J. Biol. Chem. .278, 35299-35310.

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