Helmholtz Graduate School 'Molecular Cell Biology'

MDC/Humboldt-Universität zu Berlin Groups

HU GROUPS 2010

The Max Delbrück Centre for Molecular Medicine (MDC)

The MDC is a leading research institution in the field of Molecular Medicine with around 400 publications in top international journals every year, including contributions to Science, Nature, Cell etc. It has more than 50 research groups, an exceptional research base and state-of-the-art facilities, a long-standing cooperation between basic researchers, clinical scientists and the partner universities, and can thus provide excellent training of future scientists in molecular cell biology.

The four major research areas of the MDC are: **Cancer, Cardiovascular and Metabolic Diseases, Function and Dysfunction of the Nervous System and Medical Systems Biology**.

This brochure presents our **research groups at the Humboldt-Universität zu Berlin**.

Please see the last page of this brochure for contact details of the PhD Programme coordinators.

MDC Communication Centre

The Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB)

The MDC established the Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB) in 2007 to offer a unified interdisciplinary platform for structured PhD training at the MDC and its partners. We work in collaboration with our partners the Humboldt-Universität zu Berlin (HU), the Freie Universität Berlin (FU), and the Leibniz Institute for Molecular Pharmacology (FMP). There are currently about 200 international PhD students in the Helmholtz Graduate School selected on competitive basis. For more information please visit www.mdc-berlin.de/phd.

The Graduate School furthermore offers the following **central services**:

- Travel & Collaboration Fund
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- PhD Project Committee
- Annual reviews of your project by MDC faculty and external experts.
- University interface
- Assistance with the registration at the partner universities and organisation of your PhD examination
- Social activities to make your life in one of the most vibrant and affordable of European capitals a truly stimulating and enjoyable experience!

MDC/Humboldt-Universität zu Berlin Groups

MDC Campus

Genetics

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www2.hu-berlin.de/biologie/genetics/frame_gen.html

Please note: Prof. Börner's group does not take new PhD students in the 2010 selection round.

Our group focuses on three major research areas:

Plant Molecular Biology:
- Transcription of plastidial and mitochondrial genes
- Interactions between nucleus, plastids and mitochondria

Molecular Biology of Cyanobacteria:
- Secondary metabolites
- Light perception
- Function of genes homologous to chloroplast ORFs
- Biotechnology

Molecular Genetics:
- Chloroplast Gene Expression
- Chloroplast RNA Binding Proteins
- PPR Proteins: a Large Plant-Specific RNA Binding Protein Family

Publications:

Bohne, A.-V. S. Ruf; T. Börner; R. Bock (2007) Faithful transcription initiation from a mitochondrial promoter in transgenic plastids. Nucl. Acids Res. doi: 10.1093/nar/gkm679

Ishida, K., G. Christiansen, W.Y.Yoshida, R. Kurmayer, M. Welker, J. Bonjoch, C. Hertweck, T. Börner, T. Hemscheidt, E. Dittmann (2007) Biosynthetic pathway and structure analysis of aeruginoside 126A and B, cyanobacterial peptide glycosides bearing an unusual 2-carboxy-6-hydroxyoctahydroindole moiety. Chem. Biol. 14: 565-576

Kühn, K., A.-V. Bohne, K. Liere, A. Weihe, T. Börner (2007) Arabidopsis phage-type RNA polymerases: accurate in vitro transcription of organellar genes. Plant Cell 19: 959-971

Schatz, D., Y. Kern, A. Vardi, A. Sukenik, S. Carneli, T. Börner, E. Dittmann, A. Kaplan (2007) Towards clarification of the biological role of microcystins, a family of cyanobacterial toxins. Environ. Microbiol. 9: 965-970

Swiatecka-Hagenbruch, M., K. Liere, T. Börner (2007) High diversity of plastidial promoters in Arabidopsis thaliana, Mol. Gen. Genet. 277: 725-734

Molecular Biophysics

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The research is interdisciplinary ranging from structural biology, molecular and cell biology, virology, spectroscopy to the design and synthesis of biomolecule analogues. The topics of basic and applied research are protein-mediated fusion of membranes (viral fusion proteins), virus budding, lipid-trafficking in eukaryotic cells, protein-lipid interaction in membranes, and application of membranes in nanobiotechnology. One focus of our research is an early step of cell entry of enveloped viruses. Enveloped viruses as influenza virus or HIV fuse with respective membranes to deliver their genome into the host cell. In our lab enveloped viruses are employed to study the molecular mechanism of protein-mediated virus-membrane fusion. We use various biophysical and cell biology methods to follow directly the fusion process and to identify structural intermediates mainly by fluorescence microscopy and spectroscopy. To understand the functioning of viral fusion proteins, specific mutants and chimeras of those proteins are created and probed for their fusion activity. By strong collaboration with groups specialised in electron microscopy and in image reconstruction, we identify the 3D structure of complete viral fusion protein at conditions typical for triggering membrane fusion. Another research focus is the assembly and budding of enveloped viruses. We are interested in measuring expression of viral mRNA in single cells, mechanisms underlying local enrichment of viral components at the budding site of the host membranes. Another specific interest of our group is the protein-mediated translocation of lipids across cellular membranes and their intracellular transport to distinct organelles. Although indirect evidence already exists the molecular identification of translocases pumping on the expense of energy (specific) lipids across membranes and of flippases facilitating a rapid, energy independent and unspecific movement of lipids in membranes is still awaiting. We are very much interested in the physiological relevance of those protein-mediated lipid transports and their function(s), for example in cell genesis, apoptosis, fertilisation, exo- and endocytosis, and in the enrichment of specific lipids in the bile fluid. Our joined efforts with different companies in the field of Nanobiotechnology are related to use lipophilic oligonucleotides to functionalize and to structure membranes.

Essentially, stationary and time-resolved fluorescence spectroscopy and (two photon) confocal microscopy are applied including single particle tracking, Fluorescence Lifetime Imaging, TIRFM, Fluorescence Correlation spectroscopy.

Publications:

Scolari, S., Engel, S., Krebs, N., Plazzo, A.P., De Almeida, R.F.M, Prieto, M., Veit, M., Herrmann, A. (2009) Lateral distribution of the transmembrane domain of influenza virus hemagglutinin revealed by time-resolved fluorescence imaging. J. Biol. Chem. 284, 15708-15716.

Stöckl, M., Plazzo, A.P., Korte, T., and Herrmann, A. (2008) Detection of lipid domains in model and cell membranes by fluorescence lifetime imaging microscopy of fluorescent lipid analogues. J. Biol. Chem. 283, 30828-30837.

Cell Differentiation and Tumorigenesis

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Hematopoietic stem cells in the bone marrow sustain their own maintenance and give rise to "transit amplifying", lineage committed cells that terminally differentiate into at least 8 different short-lived cell types. Hematopoietic transcription factors concertedly control cell amplification, commitment, and differentiation. Mutations in these key transcription factors dysregulate hematopoiesis and cause diseases such as leukemia, anemia, or immune defects. A major task in experimental hematology, leukemia research, and stem cell research is to untangle the underlying transcription factor network, disclose functional interactions between its components, understand how they regulate genes and chromatin, and thereby reveal novel therapeutic targets.

Major interests of the lab are the function of transcription factors of the CCAAT Enhancer Binding Protein family (C/EBPs), Myb, and Tal1/Scl during gene regulation and chromatin remodeling, and signaling events that mediate transcription factor regulation (C/EBP, Myb, Tal1/Scl, WNT-b,g-catenin/LEF). We use state-of-the-art molecular genetics and targeted mouse genetics to unravel onco-developmental processes connected to these transcription factors.

Publications:

Smink JJ; Begay V; Schoenmaker T; Sterneck E; de Vries TJ; Leutz A. Transcription factor C/EBPbeta isoform ratio regulates osteoclastogenesis through MafB. *EMBO Journal* 28 (12): 1769-1781 (2009-06-17).

Broeske AM; Vockentanz L; Kharazi S; Huska MR; Mancini E; Scheller M; Kuhl C; Enns A; Prinz M; Jaenisch R; Nerlov C; Leutz A; Andrade-Navarro MA; Jacobsen SE; Rosenbauer F. DNA methylation protects hematopoietic stem cell multipotency from myeloerythroid restriction. *Nature Genetics* : (2009-10-04).

Pless O; Kowenz-Leutz E; Knoblich M; Lausen J; Beyerman M; Walsh MJ; Leutz A. G9a-mediated lysine methylation alters the function of CCAAT/enhancer-binding protein-beta. *Journal of Biological Chemistry* 283 (39): 26357-26363 (2008-09-26).

Jeannet G; Scheller M; Scarpellino L; Duboux S; Gardiol N; Back J; Kuttler F; Malanchi I; Birchmeier W; Leutz A; Huelsken J; Held W. Long-term, multilineage hematopoiesis occurs in the combined absence of beta-catenin and gamma-catenin. *Blood* 111 (1): 142-149 (2008-01-01)

Simmons DG; Natale DR; Begay V; Hughes M; Leutz A; Cross JC. Early patterning of the chorion leads to the trilaminar trophoblast cell structure in the placental labyrinth. *Development* 135 (12): 2083-2091 (2008-06)

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Please note: not all research group leaders take PhD students in every selection round.

Molecular Parasitology

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Please note: Prof. Lucius' group does not take new PhD students in the 2010 selection round.

Our research focuses on molecular aspects of the relationship between eukaryotic parasites and the immune system of their hosts. We have characterized immunomodulatory proteins that are released by parasitic nematodes and alter the phenotype of macrophages, inhibit antigen presentation and lead to increased production of the inhibitory cytokine IL-10. Our data suggest that helminth proteins have a particular evolutionary design and down-regulate inflammatory host cell reaction by various means, in order to enhance the survival of the parasites. The mechanisms underlying these changes are studied by identification of host cell receptors, transcriptome analysis and analysis of signal transduction. Recombinant nematode immunomodulators are tested in murine models of transplantation, allergy, colitis and other inflammatory diseases in order to evaluate their potential for clinical use. We also study mechanisms of protective immunity against filarial nematodes of rodents and humans. Several recombinant vaccine candidate proteins were characterized and are now tested in animal models in order to evaluate their potential and decipher the effector mechanisms. Another focus of research is work on intracellular protozoan parasites of the genus Eimeria (dwelling intestinal epithelia) and Toxoplasma (causing disease in immunocompromised individuals) The host effector mechanisms as well as modifications of the host cell exerted by pathogens are studies in mouse models or in vitro, in order to characterize molecules and mechanisms relevant in this context.

Publications:

Lendner, M., Lucius, R., Hartmann, S. (2008) RNA interference in Heligmosomoides polygyrus: new aspects. Molecular & Biochemical Parasitology, in press.

Rzepecka, J., Rausch, S., Klotz, C., Schnöller, C., Kornprobst, T., Hagen, J., Ignatius, R. Lucius, R., Hartmann, S. (2008) Calreticulin from the intestinal nematode Heligmosomoides polygyrus is a Th2-skewing protein and interacts with murine scavenger receptor-A. Molecular Immunology, under revision.

Hartmann, S., Schnöller, C., Dahten, A., Avagyan, A., Rausch, S., Lendner, M., Bocian, C., Pillai, S., Lucius, R., Worm, M., Hamelmann, E., (2008) Gastrointestinal nematode infection interferes with experimental allergic airway inflammation but not atopic dermatitis. Clinical & Experimental Allergy, under revision.

Nuclear Signaling & Chromosomal Domains

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Cellular communication is essential for development, the control of proliferation and the maintenance of the differentiated state. For this, molecular networks evolved to relay signals received at the cell surface by transmembrane receptors to downstream effector molecules in the cytoplasm and the nucleus. In the nucleus signaling molecules change the expression state of genes in their chromatin environment by interaction with regulatory factors and chromatin modifying enzymes already in place. Malfunction of these processes causes a number of severe human diseases, most prominent different types of human tumors. Since signaling is considerably conserved in evolution, we study its principles in a more simple model organism and may later transfer our knowledge to investigate human diseases. Using Drosophila as a model our group investigates chromatin switches that are crucial for Notch and TGF-b signal transduction.

A different project concerns the structure and regulation of interphase chromosome organization. Interphase chromosome structure is inherited over cell generations as seen by the pattern of bands and interbands on polytene chromosomes, that reproducibly forms in different tissues and stages of development. The open chromatin of interbands is established by proteins with specific structural and enzymatic properties and is stabilized by elements insulating the spreading of nearby condensed chromatin. Starting from the molecularly characterized interband protein Z4 [6], the aim of the project was to study the role and mechanistic interaction of interband specific proteins in establishing open chromatin structure [4,5]. General mechanisms of boundary formation between chromosomal band/interband domains and in the formation of insulator elements were another focus of our project [1,2].

Publications:

Bartkuhn, M., Straub, T., Herold, M., Herrmann, M., Rathke, C., Saumweber, H., Gilfillan, G.S., Becker, P.B., Renkawitz, R. (2009) EMBO J. 28(7):877-88.

Mohan, M., Bartkuhn, M., Herold, M., Philippen, A., Heinl, N., Leers, J., White, R. A. H., Renkawitz-Pohl, R., Saumweber, H., Renkawitz, R. (2007) The Drosophila insulator protein dCTCF links enhancer blocking to body patterning. EMBO J 26, 4203-4214.

Guljamow, A, Jenke-Kodama, H., Bouchier, C., Tandeau de Marsac, N. Saumweber, H., Dittmann, E. (2007) Horizontal gene transfer of two cytoskeletal elements from a eukaryote to a cyanobacterium. Current Biology 17, R757-R759.

Mendjan, S, Taipale, M, Kind, J, Holz, H, Gebhard, P, Schelder, M, Vermeulen, M, Buscaino, A, Duncan, K, Mueller, J, Wilm, M, Stunnenberg, H, Saumweber, H and Akhtar, A (2006) Nucleoporins are involved in the transcriptional regulation of dosage compensation in Drosophila. Mol Cell 21.

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Intracellular Proteolysis

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Protein biogenesis is a remarkably imperfect process. About one third of all newly synthesized proteins are presumably defective. Functional proteins that were damaged by heat, oxidizing conditions or toxic agents further increase the pool of aberrant polypeptides. Defective proteins are toxic to cells and must be properly taken care of. Accordingly, cellular chaperones identify and repair deviant proteins. When salvage is not possible, the ubiquitin -proteasome pathway eliminates the faulty elements. These so-called protein quality control (PQC) pathways are found in most cellular compartments. A major PQC pathway is found in the Endoplasmic Reticulum (ER) and prevents the accumulation of malfolded or unassembled proteins in the secretory pathway. Dysfunctions in this system lead to severe diseases and, in addition, some viruses highjack this system to establish themselves in the infected cell.

Publications:

Neuber, O., Jarosch,E., Volkwein, C., Walter, J., and Sommer, T. (2005) Ubx2/Sel1p links the Cdc48p/p97-Complex to Endoplasmic Reticulum Associated Protein Degradation. Nature Cell Biol., 7, 993-998.

Gauss, R, Jarosch, E, Sommer, T, and Hirsch, C. (2006) A complex of Yos9p and the HRD ligase integrates endoplasmic reticulum quality control into the degradation machinery. Nature Cell Biol., 8,849-854

Hirsch, C, Gauss, R, and Sommer T. (2006) Coping with stress: cellular relaxation techniques. Trends Cell Biol. 16, 657-63.

Clerc, S., Hirsch, C., Oggier, D. M., Deprez, P., Jakob, C., Sommer, T., and Aebi, M. (2009) HTM1 protein generates the N-glycan signal for glycoprotein degradation in the endoplasmic reticulum. J. Cell. Biol. 184, 159-172

Hirsch, C., Gauss, R., Horn, S.C., Neuber, O., and Sommer, T. (2009) The ubiquitylation machinery of the endoplasmic reticulum. Nature 458, 453-460.

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Molecular Cell Biology and Gene Therapy

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My research interests lies in the therapy of cancer and viral diseases using T cell receptor (TCR) gene therapy. We address questions related to: generation of T cells with new antigen specificity, modification of TCR genes to generate T cells with high functional avidity, safety aspects of TCR gene-modified T cells with respect to the recognition of self-antigens, adoptive transfer of TCR gene-modified T cells in mice as preclinical models, and optimization of TCR transfer vectors.

Currently there are 5 graduate students in my lab with 3 completed dissertations since 2005. Per year I am involved in ~15 theses defenses at the Humboldt University Berlin. My teaching duties include lectures on molecular cell biology and gene therapy as well as theoretical and Practical Courses on these topics.

Publications:

Uckert, W., Schumacher, T. (2009). TCR transgenes and transgene cassettes for TCR gene therapy: status in 2008. Cancer Immunol. Immunother. 58: 809-822.

Leisegang, M., Engels, B., Meyerhuber, P., Kieback, E., Sommermeyer, D., Xue, S.-A., Reuß, S., Stauss, H., Uckert, W. (2008). Enhanced functionality of T cell receptor-redirected T cells is defined by the transgene cassette. J. Mol. Med. 86: 573-583.

Kieback, E., Charo, J., Sommermeyer, D., Blankenstein, T., Uckert, W. (2008). A safeguard eliminates T cell receptor gene-modified autoreactive T cells after adoptive transfer. Proc. Natl. Acad. Sci. USA, 105: 623-628.

Reuss, S., Biese, P., Cosset, F.L., Takeuchi, Y., Uckert, W. (2007). Suspension packaging cell lines for the simplified generation of T cell receptor encoding retrovirus vector particles. Gene Therapy 14, 595-603.

Sommermeyer, D., Neudorfer, J., Weinhold, M., Leisegang, M., Charo, J., Engels, B., Nößner, E., Heemskerk, M., Schendel, D.J., Blankenstein, T., Bernhard, H., Uckert, W. (2006). Designer T cells by T cell receptor replacement. Eur. J. Immunol. 36, 3052-3059.

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TransCard Helmholtz Research School

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