Helmholtz Graduate School 'Molecular Cell Biology'

MDC Cancer and Affiliated Groups

CANCER GROUPS 2010

The Max Delbrück Centre for Molecular Medicine (MDC)

MDC Communication Centre

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 **Cancer research groups**. The MDC Cancer groups work in the fields of signal transduction and growth control, structural genome research and tumor immunology and collaborate closely with the Robert-Rössle Cancer Clinic of the Charité/ Humboldt-Universität zu Berlin, and the Helios-Clinic.

The objectives are to understand the development and the progression of cancer diseases through excellent basic research at the molecular level, to develop improved diagnostics, and finally to utilize the gained knowledge for the development of new treatments.

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

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
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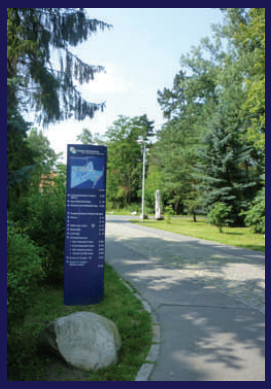

MDC Campus

Signal Transduction, Invasion & Metastasis of Epithelial Cells

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Our laboratory concentrates on the molecular analysis of epithelial morphogenesis and differentiation. In previous years, we defined the adhesion and signalling capacities of the E-cadherin/catenin/Wnt system. We have studied Wnt/beta-catenin signaling in the heart, and established a link between the beta-catenin homologue, plakophilin 2, and heart morphogenesis. Moreover, we have investigated the role of scatter factor/ hepatocyte growth factor (SF/HGF) and its receptor, the c-met tyrosine kinase, in morphogenesis of epithelial cells.

Publications:

Klaus, A., Saga, Y., Taketo, M. M., Tzahor, E., and Birchmeier, W. (2007). Distinct roles of Wnt/beta-catenin and Bmp signaling during early cardiogenesis. PNAS, 104, 18531-18536.

Moeller, H., Jenny, A., Schaeffer, H. J., Schwarz-Romond, T., Mlodzik, M., Hammerschmidt, M., and Birchmeier, W. (2006). Diversin regulates heart formation and gastrulation movements in development. PNAS, 103, 15900-15905.

Stelzl, U., Worm, U., Lalowski, M., Haenig, C., Brembeck, F. H., Goehler, H., Stroedicke, M., Zenkner, M., Schoenherr, A., Koeppen, S., Timm, J., Mintzlaff, S., Abraham, C., Bock, N., Kietzmann, S., Goedde, A., Toksöz, E., Droege, A., Krobitsch, S., Korn, B., Birchmeier, W., Lehrach, H., and Wanker, E. E. (2005). A human protein-protein interaction network: a resource for annotating the proteome. Cell, 122, 957-968.

Grossmann, K., Grund, C., Hülsken, J., Behrend, M., Erdmann, B., Franke, W.W., and Birchmeier, W. (2004): Requirement of plakophilin 2 for heart morphogenesis and cardiac junction formation. J. Cell Biol. 167, 149-160.

Gerull, B., Heuser, A., Wichter, T., Paul, M., Basson, C.T., McDermott, D.A., Lerman, B.B., Markowitz, S.M., Ellinor, P.T., MacRae, C.A., Peters, S., Grossmann, K., Michely, B., Sasse-Klaassen, S., Birchmeier, W., Dietz, R., Breithardt, G., Schulze -Bahr, E., and Thierfelder, L. (2004): Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nature Genetics 36, 1162-1164.

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TransCard Helmholtz Research School

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

Molecular Immunology and Gene Therapy

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Most of the current experimental cancer models do not reflect the pathophysiology of real-life cancer. Cancer usually occurs sporadically and is clonal in origin. Between tumor initiation and progression clinically unapparent pre-malignant cells may persist for years or decades in humans. More recently, mouse models of sporadic cancer have been developed. The mouse germ-line can be engineered with high precision so that defined genes can be switched on and off in the adult organism, ideally in a locally and timely controlled fashion. However, analysis of the immune response against sporadic tumors requires the knowledge of a tumor antigen.

Publications:

Kruschinski A; Moosmann A; Poschke I; Norell H; Chmielewski M; Seliger B; Kiessling R; Blankenstein T; Abken H; Charo J: Engineering antigen-specific primary human NK cells against HER-2 positive carcinomas, Proceedings of the National Academy of Sciences of the United States of America 105 (45): 17481-17486 (2008-11-11)

Willimsky G; Czeh M; Loddenkemper C; Gellermann J; Schmidt K; Wust P; Stein H; Blankenstein T: Immunogenicity of premalignant lesions is the primary cause of general cytotoxic T lymphocyte unresponsiveness, Journal of Experimental Medicine 205 (7): 1687-1700 (2008-07-07)

Kieback E; Charo J; Sommermeyer D; Blankenstein T; Uckert W: A safeguard eliminates T cell receptor gene-modified autoreactive T cells after adoptive transfer, Proceedings of the National Academy of Sciences of the United States of America 105 (2): 623-628 (2008-01-15)

Blankenstein T: Do autochthonous tumors interfere with effector T cell responses? Seminars in Cancer Biology 17 (4): 267-274 (2007-08)

Willimsky G; Blankenstein T: The adaptive immune response to sporadic cancer, Immunological Reviews 220 (1): 102-112 (2007-12)

Cayeux S; Bukarica B; Buschow C; Charo J; Bunse M; Doerken B; Blankenstein T: In vivo splenic CD11c cells down-regulate CD4 T-cell response thereby decreasing systemic immunity to gene-modified tumour cell vaccine, Gene Therapy 14 (20): 1481-1491 (2007-10)

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Clinical and Molecular Oncology

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Cell death and cell cycle deregulation in cancer and resistance to anticancer therapy. Virtually all medical anticancer therapies rely on the induction of cell cycle arrest or cell death in the malignant cells. Consequently, the analysis of such genetic events allows for the identification of patients at risk for an insufficient response to treatment with e.g. chemotherapeutic drugs or ionising irradiation, and poor survival. Such analyses provide a rational basis for a molecular understanding of the response to anticancer therapies and the clinical use of cancer therapeutics. The aim of the group is, therefore, to define genetic defects in cancer that result in aggressive disease, poor prognosis, and resistance to clinical cancer therapy. To this end, we have established an extensive genotyping program in solid tumors and leukemias. Recent pharmacogenomic data obtained from these screenings depict that defects in central regulatory genes, e.g. of the p53 pathway, do not result in global resistance to therapy but may be overcome by adequate therapeutic modalities. Functional consequences of such cell death and cell cycle defects are analysed in vitro, often by the use of adenoviral gene transfer for complementation of disrupted genes. In addition, these systems are exploited to gain insights into novel aspects of cell cycle and cell death regulation and their intricate interactions.

Publications:

Gillissen B, Essmann F, Hemmati P, Richter A, Richter A, Öztop I,Chinnadurai G, Dörken B and Daniel PT.(2007). Mcl-1 mediates the Bax dependency of Nbk/Bik-induced apoptosis. J Cell Biol. 179, 701-715.

Hemmati, PG, Güner D, Gillissen B, Wendt J, von Haefen C, Chinnadurai G, Dörken B, Daniel PT. (2006). Bak functionally complements for loss of Bax during p14ARF-induced mitochondrial apoptosis in human cancer cells. Oncogene. 25, 6582-94.

Daniel PT, Koert U, Schuppan J. (2006). Apoptolidin: induction of apoptosis by a natural product. Angew Chem Int Ed Engl. 45, 872-93.

Sturm I, Stephan C, Gillissen B, Siebert R, Janz M, Radetzki S, Jung K, Loening S, Dörken B, Daniel PT. (2006) .Loss of the tissue-specific proapoptotic BH3-only protein Nbk/Bik is a unifying feature of renal cell carcinoma. Cell Death Differ. 13, 619-27.

Gillissen B, Essmann F, Graupner V, Stärck L, Radetzki S, Dörken B, Schulze-Osthoff K, Daniel PT. (2003). Induction of cell death by the BH3-only Bcl-2 homolog Nbk/Bik is mediated by an entirely Bax-dependent mitochondrial pathway. EMBO J. 22, 3580-90.

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G-proteins in membrane remodelling

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Guanine nucleotide binding proteins (G-proteins) are involved in a diverse range of cellular processes including protein synthesis, sensual perception, vesicular transport and signal transduction cascades. Whereas small G-proteins are molecular switches that cycle between an active GTP-bound form and an inactive GDP-bound form, large G-proteins of the dynamin superfamily are mechano-chemical enzymes that use the energy of GTP hydrolysis to actively remodel membranes. Members of both groups bind to membranes, and this interaction is crucial for their function. Our projects aim to elucidate the interaction and reciprocal modulation of membranes and G-proteins using structural, biochemical and cell-biological methods.

Publications:

Selbach, M, Paul FE, Brandt S, Guye, P, Daumke, O, Backert, S, Dehio, C, Mann M. (2009) Host cell interactome of tyrosine-phosphorylated bacterial proteins. Cell Host Microbe, 5, 397-403.

Daumke, O, Lundmark R, Vallis, Y, Martens, S, Butler, PJ, McMahon HM. (2007) Architectural and mechanistic insights into an EHD ATPase involved in membrane remodelling. Nature, 449, 923-927.

Henne, WM, Kent, HM, Ford, MG, Hegde, BG, Daumke, O, Butler, PJ, Mittal, R, Langen, R, Evans, PR, McMahon, HT. (2007) Structure and analysis of FCHo2 F-BAR domain: A dimerizing and membrane recruitment module that effects membrane curvature. Structure, 15, 839-852.

Kupzig, S, Deaconescu, D, Bouyoucef, D, Walker SA, Liu Q, Polte, CL, Daumke, O, Ishizaki, T, Lockyer, PJ, Wittinghofer, A, Cullen PJ. (2006) GAP1 family members constitute bifunctional RAS and RAP GTPase-activating proteins. J Biol Chem, 281, 9891-9900.

Daumke, O, Weyand , M, Chakrabarti PP, Vetter I, Wittinghofer A. (2004). The GTPase‐activating protein Rap1GAP uses a catalytic asparagine. Nature, 429, 197-201.

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Haematoloy, Oncology and Tumorimmunology

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Studying the molecular mechanisms underlying B cell development and differentiation is one of the key approaches to understanding the pathways leading to disease. We are particularly interested in terminally differentiated B cells that give rise to hematologic malignancies like Hodgkin lymphoma and multiple myeloma. Hodgkin- and Reed-Sternberg cells are tumor cells of classical Hodgkin lymphoma (cHL). In most cases, they are derived from germinal center B cells. However, they do not express immunoglobulins and typical B cell-specific markers. We focus our work on the characterization of the molecular basis for the dedifferentiated B cell phenotype of Hodgkin lymphoma and aim to identify molecular defects that are responsible for tumor cell transformation and differentiation. We further evaluate molecular defects in lymphomas related to Hodgkin lymphoma like anaplastic large cell lymphoma (ALCL), primary effusion lymphoma (PEL) or multiple myeloma. It is the ultimate aim of our work to identify targets for the development of new treatment strategies.

Publications:

le Coutre P; Meisel H; Hofmann J; Roecken C; Vuong GL; Neuburger S; Hemmati PG; Doerken B; Arnold R. Reactivation of hepatitis E infection in a patient with acute lymphoblastic leukaemia after allogeneic stem cell transplantation. *Gut* 58 (5): 699-702 (2009-05).

le Coutre P; Reinke P; Neuhaus R; Trappe R; Ringel F; Lalancette M; Hemmati PG; Doerken B; Daniel PT. BCR-ABL positive cells and chronic myeloid leukaemia in immune suppressed organ transplant recipients. *European Journal of Haematology* : (2009-10-03).

Westermann J; Hecker AC; Floercken A; Doerken B; Pezzutto A, Granulocyte macrophage-colony stimulating factor plus interleukin-2 plus alpha-interferon plus 5-fluorouracil in the treatment of metastatic renal cell cancer: induction of CD80/86+ T cells indicates adverse outcome. *Journal of Immunotherapy* 32 (6): 667-675 (2009-07).

Rehm A; Anagnostopoulos I; Gerlach K; Broemer M; Scheidereit C; Joehrens K; Huebler M; Hetzer R; Stein H; Lipp M; Doerken B; Hoepken UE. Identification of a chemokine receptor profile characteristic for mediastinal large B-cell lymphoma. *International Journal of Cancer* 125 (10): 2367-2374 (2009-11-15).

Pelzer U; Stieler J; Roll L; Hilbig A; Doerken B; Riess H; Oettle H. Second-line therapy in refractory pancreatic cancer. results of a phase II study. *Onkologie* 32 (3): 99-102 (2009-03).

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Experimental Pharmacology

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The main area of investigations performed within the period of report concerns translational research and was focused on the definition of biomarkers for and testing of novel anticancer agents. Several patient-derived xenografts of leukemias, breast, colon, ovarian and lung cancers were established and characterized regarding compliance with the clinical situation, histology and chemotherapeutic response. These models were further analyzed concerning the involvement of target molecules in the biology of tumors or treatment responses.In vivo approaches were used as well to investigate the efficacy of a novel antimetastatic agent. This has been developed with the aim to influence the interaction of tumor cells with blood and endothelial cells by targeted liposomes. These were shown to stimulate the formation of platelet-tumor cell complexes in the vasculature and to influence the process of metastasis. The in vivo situation also was a precondition for investigations concerning the engraftment and differentiation of human stem cells. Working with adult cord blood derived CD34-positive cells we could show that a differential distribution in immunodeficient mice was obtained by pre-treating the cells with selected cytokines or by direct cell-to-cell contact. An ongoing project especially focuses on the potential of adult and embryonic stem cells for liver regeneration.

Publications:

Diaz Miqueli A; Rolff J; Lemm M; Fichtner I; Perez R; Montero E. Radiosensitisation of U87MG brain tumours by anti-epidermal growth factor receptor monoclonal antibodies. *British Journal of Cancer* 100 (6): 950-958 (2009-03-24)

Fritzmann J; Morkel M; Besser D; Budczies J; Kosel F; Brembeck FH; Stein U; Fichtner I; Schlag PM; Birchmeier W. A colorectal cancer expression profile that includes transforming growth factor ss inhibitor BAMBI predicts metastatic potential. *Gastroenterology* 137 (11): 165-175 (2009-07)

Hoffmann J; Fichtner I; Lemm M; Lienau P; Hess-Stumpp H; Rotgeri A; Hofmann B; Klar U. Sagopilone crosses the blood -brain barrier in vivo to inhibit brain tumor growth and metastases. *Neuro Oncology* 11 (2): 158-166 (2009-04)

Graeser R; Esser N; Unger H; Fichtner I; Zhu A; Unger C; Kratz F. INNO-206, the (6-maleimidocaproyl hydrazone derivative of doxorubicin), shows superior antitumor efficacy compared to doxorubicin in different tumor xenograft models and in an orthotopic pancreas carcinoma model. *Investigational New Drugs* : (2009-01-08)

Heringer-Walther S; Eckert K; Schumacher SM; Uharek L; Wulf-Goldenberg A; Gembardt F; Fichtner I; Schultheiss HP; Rodgers K; Walther T. Angiotensin-(1-7) stimulates hematopoietic progenitor cells in vitro and in vivo. *Haematologica* 94 (6): 857-860 (2009-06)

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Macromolecular Structure and Interaction

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The inner workings of the cells forming healthy or diseased organisms are governed by the interplay of thousands of large and small molecules. The activities of these molecules – proteins, nucleic acids, carbohydrates, lipids, membranes and small metabolites – are tightly regulated in time and space. They can be described according to the concept of functional modules: defined units of cellular activity that assemble into discrete, stable entities during function and often undergo cyclic structural rearrangements. A functional module is charac-ter-ized by its supramolecular architecture and the time domain within which it functions. It receives a specific input and delivers an appropriate output to the cell. Some functional modules are best described as molecular machines, whereas others are characterized by a dynamic assembly and disassembly of their constituent parts. Our laboratory focusses on structural analyses of functional modules using macromolecular crystal-lo-graphy as its central method. This approach implies that we primarily address the lower levels of modular organisation which carry out molecular and sub-modular functions. Structural data must be combined with time-resolved functional analyses and theory to yield proper insight into modular function.

Publications:

Guenther UP; Handoko L; Varon R; Stephani U; Tsao CY; Mendell JR; Luetzkendorf S; Huebner C; von Au K; Jablonka S; Dittmar G; Heinemann U; Schuetz A; Schuelke M. Clinical variability in distal spinal muscular atrophy type 1 (DSMA1): determination of steady-state IGHMBP2 protein levels in five patients with infantile and juvenile disease. *Journal of Molecular Medicine* 87 (1): 31-41 (2009-01)

Koenig B; Mueller JJ; Lanka E; Heinemann U. Crystal structure of KorA bound to operator DNA: insight into repressor cooperation in RP4 gene regulation. *Nucleic Acids Research* 37 (6): 1915-1924 (2009-04)

Hannemann F; Guyot A; Zoellner A; Mueller JJ; Heinemann U; Bernhardt R. The dipole moment of the electron carrier adrenodoxin is not critical for redox partner interaction and electron transfer. *Journal of Inorganic Biochemistry* 103 (7): 997-1004 (2009-07)

Thoms S; Max KE; Wunderlich M; Jacso T; Lilie H; Reif B; Heinemann U; Schmid FX. Dimer formation of a stabilized Gbeta1 variant. A structural and energetic analysis. *Journal of Molecular Biology* 391 (5): 918-932 (2009-09-04)

Kumar V; Roske Y; Singh N; Heinemann U; Singh TP; Yadav S. Purification and preliminary X-ray crystallographic studies of beta-microseminoprotein from human seminal plasma. *Acta Crystallographica Section* F 65 (5): 518-521 (2009-05-01)

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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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Molecular Tumor Genetics and Immunogenetics

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Our group is interested in the field of immune regulation, immunopathogenesis, tumor genetics, and translational immunology with focus on the following major areas:

- The role of homeostatic chemokine receptors in lymphoid organ development, systemic immune responses, and chronic inflammatory diseases.
- Differentiation, trafficking and function of memory/effector T cells, especially the role of follicular B helper T cells in inflammation and autoimmunity.
- Immunomodulatory and oncogenic functions of herpesvirus-encoded chemokine receptors.
- The function of sphingophospholipid receptors in the immune system.
- Target identification and validation in preclinical animal models with focus on B cell lymphoma and gastric carcinoma.

Publications:

Nitta T; Nitta S; Lei Y; Lipp M; Takahama Y. CCR7-mediated migration of developing thymocytes to the medulla is essential for negative selection to tissue-restricted antigens. Proceedings of the National Academy of Sciences of the United States of America 106 (40): 17129-17133 (2009-10-06).

Achtman AH; Hoepken UE; Bernert C; Lipp M. CCR7-deficient mice develop atypically persistent germinal centers in response to thymus-independent type 2 antigens. Journal of Leukocyte Biology 85 (3): 409-417 (2009-03).

Buonamici S; Trimarchi T; Ruocco MG; Reavie L; Cathelin S; Mar BG; Klinakis A; Lukyanov Y; Tseng JC; Sen F; Gehrie E; Li M; Newcomb E; Zavadil J; Meruelo D; Lipp M; Ibrahim S; Efstratiadis A; Zagzag D; Bromberg JS; Dustin ML; Aifantis I. CCR7 signalling as an essential regulator of CNS infiltration in T-cell leukaemia. Nature 459 (7249): 1000-1004 (2009-06-18).

van de Pavert SA; Olivier BJ; Goverse G; Vondenhoff MF; Greuter M; Beke P; Kusser K; Hoepken UE; Lipp M; Niederreither K; Blomhoff R; Sitnik K; Agace WW; Randall TD; de Jonge WJ; Mebius RE. Chemokine CXCL13 is essential for lymph node initiation and is induced by retinoic acid and neuronal stimulation. Nature Immunology : (2009-09-27).

Rehm A; Anagnostopoulos I; Gerlach K; Broemer M; Scheidereit C; Joehrens K; Huebler M; Hetzer R; Stein H; Lipp M; Doerken B; Hoepken UE. Identification of a chemokine receptor profile characteristic for mediastinal large B-cell lymphoma. International Journal of Cancer 125 (10): 2367-2374 (2009-11-15).

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Molecular Immunotherapy

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The goal of our work is the implementation of basic research into preclinical models and clinical trials. A first strategy is based on the induction of cancer immune responses by vaccination. A pilot clinical study with a genemodified tumor cell vaccine for treatment of advanced renal cancer has been concluded, a follow-up study with simultaneous administration of an antibody against regulatory T-cells is in preparation. A phase I Dendritic cell vaccination study in chronic myeloid leukemia has also been successfully concluded, leading to a multicenter clinical trial in patients with persisting minimal residual disease after imatinib treatment, due to start in 2008. These clinical studies are flanked by preclinical animal models of DNA vaccination whereby vectors coding for cytokines or the chemokines CCL19 and CCL21 lead to an improved stimulation of antigen presenting cells / T-cells. With the aim of improving immunity against the adenocarcinoma-associated EpCAM antigen we have generated mutated, heteroclitic peptides of EpCAM that display a high immunogenicty. These peptides are being evaluated for clinical use. A further strategy is T-cell receptor gene transfer for adoptive therapy of Lymphomas. Transgenic T-cells that use the T-cell receptors of EBV-specific CD8 and CD4 T-cell clones are being developed for adoptive immunotherapy of EBV associated diseases such as Hodgkin's Disease and Post-Transplant Lymphoproliferative Disorders (PTLDs). Epitopes of the B-cell antigens CD19 and CD20 are also being evaluated as targets for TCR transgenic T-cells.

Publications:

Schmetzer, O, Moldenhauer, G, Riesenberg, R, Pires, JR, Schlag, P, Pezzutto, A. (2005). Quality of recombinant protein determines the amount of autoreactivity detected against the tumorassociated epithelial cell adhesion molecule antigen: low frequency of antibodies against the natural protein. J Immunol. 174, 942-952.

Westermann, J, Lessen, A, Schlimper, C, Baskaynak, G, Le Coutre, P, Dörken, B, Pezzutto A. (2006). Simultaneous cytokine analysis by cytometric bead array for the detection of leukaemia- reactive T-cells in patients with chronic myeloid leukaemia. Br J Haematol. 132, 32-35.

Sebelin-Wulf, K, Nguyen, TD, Oertel, S, Papp-Vary, M, Trappe, RU, Schulzki, A, Pezzutto, A, Riess, H, Subklewe, M. (2007). Quantitative analysis of EBV-specific CD4/CD8 T cell numbers, absolute CD4/CD8 T cell numbers and EBV load in solid organ transplant recipients with PLTD. Transpl Immunol. 17, 203-210.

Westermann, J, Nguyen-Hoai, T, Baldenhofer, G, Hopken, UE, Lipp, M, Dörken, B, Pezzutto, A. (2007). CCL19 (ELC) as an adjuvant for DNA vaccination: induction of a TH1-type T-cell response and enhancement of antitumor immunity. Cancer Gene Ther. 14, 523-532.

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Cancer, Stem Cells, and Transcription Factors

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In recent years, great progress has been made in elucidating the stem and progenitor cell hierarchy of the hematopoietic system. The step-wise adoption of a cellular lineage identity during hematopoietic differentiation is preceded by the ordered reorganization of the chromatin, which is mediated by both genetic and epigenetic factors. Transcription factors are key determinants in the orchestration of cellular identity and differentiation fates through expression modulation of specific target gene subsets. Most transcription factors show narrow celllineage-and stage-restricted expression patterns, indicating the requirement for tight regulation of their activities. Moreover, if dysregulated or mutated, these transcription factors cause the differentiation block observed in many leukaemias. Using mouse genetics as well as biochemical approaches, our research group is particularly interested in the activities and transcriptional regulation of main hematopoietic transcription factors, such as PU.1, and in their functional interplay with epigenetic chromatin modifiers.

Publications:

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Steidl U; Steidl C; Ebralidze A; Chapuy B; Han HJ; Will B; Rosenbauer F; Becker A; Wagner K; Koschmieder S; Kobayashi S; Costa DB; Schulz T; OBrien KB; Verhaak RG; Delwel R; Haase D; Truemper L; Krauter J; Kohwi-Shigematsu T; Griesinger F; Tenen DG. A distal single nucleotide polymorphism alters long-range regulation of the PU.1 gene in acute myeloid leukemia. Journal of Clinical Investigation 117 (9): 2611-2620 (2007-09)

Rosenbauer F; Tenen DG. Transcription factors in myeloid development: balancing differentiation with transformation. Nature Reviews Immunology 7 (2): 105-117 (2007-02)

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Signal Transduction in Tumor Cells

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A central interest of our laboratory is the regulation of gene expression by cellular signal transduction processes. "Nuclear factor kappaB" (NF-kB) is a transcription factor whose activity is controlled by inhibitory IkB proteins and IkB kinases (IKK). NF-kB/IKK signaling cascades have wide physiological and medical relevance. A major effort is to decipher the mechanisms and structures that determine gene regulation by IKK and NF-kB, the crosstalk with other gene regulatory systems and to dissect both, the role in development and in the pathogenesis of diseases.

Publications:

Schneider MR; Schmidt-Ullrich R; Paus R. The hair follicle as a dynamic miniorgan. Current Biology 19 (3): R132-T142 (2009-02-10)

Zhang Y; Tomann P; Andl T; Gallant NM; Huelsken J; Jerchow B; Birchmeier W; Paus R; Piccolo S; Mikkola ML; Morrisey EE; Overbeek PA; Scheidereit C; Millar SE; Schmidt-Ullrich R. Reciprocal requirements for EDA/EDAR/NF-kappaB and Wnt/beta-catenin signaling pathways in hair follicle induction. Developmental Cell 17 (1): 49-61 (2009-07)

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Henke N; Schmidt-Ullrich R; Dechend R; Park JK; Qadri F; Wellner M; Obst M; Gross V; Dietz R; Luft FC; Scheidereit C; Mueller DN. Vascular endothelial cell-specific NF-kappaB suppression attenuates hypertension-induced renal damage. Circulation Research 101 (3): 268-276 (2007-08-03)

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TransCard Helmholtz Research School

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Surgical Oncology

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Our group established predictive and prognostic gene signatures and expression profiles for analysis of metastases and drug resistance in colorectal cancer. The data provide the basis for novel therapeutic concepts in tumor treatment that are applicable and validated in the clinic. We were successful in identifying new metastases-associated genes, their importance for cancer metastases and their function in signaling pathways. We isolated and characterized the new gene MACC1, revealed S100A4/metastasin as novel target gene of the b-catenin pathway and analyzed the interplay of BMP-4 and Bambi in the context of b-catenin signaling. This provided insights into the tight association between early and late events of the metastasis process particularly in colorectal cancer. In collaboration with the groups of W. Birchmeier and M. Lipp achievements were made in the identification of patient-individualized gene expression profiles for improved diagnosis and prediction regarding metastases formation and patient survival. In addition to the progress made in molecular biological research, we were able to significantly advance in the development of the nonviral in vivo gene transfer for effective local cancer gene therapy. The establishment of the applicable jet-injection based gene transfer technology led to the initiation of the clinical testing in a "proof of principle" phase I trial. Moreover, we developed and tested efficient therapy-controllable vector systems for conditional transgene expression. These vectors will be employed in a multimodal therapeutic setting, combining nonviral gene therapy with chemotherapy or hyperthermia.

Publications:

Stein U, Walther W, Arlt F, Schwabe H, Smith J, Fichtner I, Birchmeier W, Schlag PM. (2008) MACC1, a newly identified key regulator of HGF/Met signaling, is a powerful predictor of colon cancer metastasis. Nat. Med. 15: 59-67.

Walther W, Siegel R, Kobelt D, Knösel T, Dietel M, Bembenek A, Aumann J, Schleef M, Baier R Stein U, Schlag PM. (2008) Novel jet-injection technology for nonviral intratumoral gene transfer in patients with melanoma and breast cancer. Clin. Cancer Res. 14: 7545-7553.

Walther W, Arlt F, Fichtner I, Aumann J, Stein U, Schlag PM. (2007) Heat-inducible in vivo gene therapy of colon carcinoma by human mdr1 promoter-regulated tumor necrosis factor alpha expression. Mol. Cancer Ther. 6, 236-243.

Jüttner S, Wissmann C, Jöns T, Vieth M, Hertel J, Gretschel S, Schlag PM, Kemmner W, Höcker M. (2006) Vascular endothelial growth factor-D and its receptor VEGFR-3: Two novel independent prognostic markers in gastric adenocarcinoma. J. Clin. Oncol. 24, 228-240.

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

Cancer Genetics and Cellular Stress Responses

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Our research program is driven by our interest in cellular stress responses (so called 'failsafe mechanisms') that may serve as anti-tumor barriers when challenged by transforming oncogenes, and, in turn, must be bypassed or inactivated before a full-blown malignancy can actually form. Importantly, ultimate stress responses such as apoptosis or cellular senescence – both terminal 'cell-cycle exit' programs – do not only counter tumorigenesis, but are utilized as chemotherapy- induced stress responses as well. Hence, principles of oncogenesis and mechanisms of treatment sensitivity seem to critically overlap and impinge on each other during tumor formation, cancer therapy and relapsed or progressive disease conditions. To test the impact of genetic lesions in cellular stress response programs on tumor development and treatment outcome under most physiological conditions in vivo, we generate mouse models harboring lymphomas (and other tumor entities) with defined genetic lesions.

Publications:

Schmitt CA. Cellular senescence and cancer treatment. Biochimica et Biophysica Acta - Reviews on Cancer 1775 (1): 5-20 (2007-01)

Reimann M; Loddenkemper C; Rudolph C; Schildhauer I; Teichmann B; Stein H; Schlegelberger B; Doerken B; Schmitt CA. The Myc-evoked DNA damage response accounts for treatment resistance in primary lymphomas in vivo. Blood 110 (8): 2996-3004 (2007-10-15)

Bouchard C; Lee S; Paulus-Hock V; Loddenkemper C; Eilers M; Schmitt CA. FoxO transcription factors suppress Myc-driven lymphomagenesis via direct activation of Arf. Genes & Development 21 (21): 2775-2787 (2007-11-01)

Braig M; Schmitt CA. Oncogene-induced senescence: putting the brakes on tumor development. Cancer Research 66: 2881-2884 (2006-03-15)

Helmrich A; Lee S; O'Brien P; Doerken B; Lowe SW; Schroeck E; Schmitt CA. Recurrent chromosomal aberrations in INK4a/ARF defective primary lymphomas predict drug responses in vivo. Oncogene 24: 4174-4182 (2005-01-01)

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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.

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

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.

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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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Genetics of Tumor Progression and Metastasis

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This is a Marie Curie Excellence Grant funded research group.

Much evidence points toward the fact that cell cycle, differentiation and tumor suppression are innately connected processes. This is based on observations that in many tumors uncontrolled proliferation, inappropriate developmental programs or de-differentiation are observed simultaneously. In addition, this finding is apparent in stem cells. In no other cellular system is such a strict control of different processes more apparent. To dissect the molecular determinants of these processes, we are focussing on mouse embryonic stem cells (mES-cells) as model system. These cells are able to be differentiate easily, form tumors and can be used to make a genetically engineered mouse. Since in most if not all human tumors it is the signalling pathway of the retinoblastoma tumorsuppressor protein (pRB) which is lost or mutated, we believe that this pathway may be the critical hinge to understand molecularly the connection of cell-cycle, differentiation and tumor suppression. Thus, we are dissecting pRB and its downstream executer the E2F family using genetic and biochemical means in differentiated as well as in stem cells. Among the E2F-family we focus on E2F3. It is the most interesting of the E2Fs: its activity is the most critical of all E2Fs for proliferation and onset of senescence. In addition, E2F3 amplification is able to cooperate with pRB-loss in human tumors. E2F3 amplification and pRB-loss promote tumor growth and invasiveness in prostate, bladder and retinoblastomas and possibly other human tumors. Understanding of the intricate relationship of pRB/E2F3 thus may increase our chance to understand and treat human cancers.

Publications:

Tapon N; Ziebold U (2008) Invasion and metastasis: stem cells, screens and survival. EMBO Reports 9 (11)

Ziebold, U, Caron, A, Bronson, R, Lees, JA. (2003). E2F3-loss has opposing effects on different pRb-deficient tumors, resulting in suppression of pituitary tumors but metastasis of medullary thyroid carcinomas. Mol. Cell. Biol. 18, 6542-6552.

Lee, EY, Cam, H, Ziebold, U, Rayman, JB, Lees, JA, Dynlacht, BD. (2002). E2F4 Loss suppresses Tumorigenesis in RB Mutant Mice Through a Novel Mechanism. Cancer Cell 2, 463-472.

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