Helmholtz Graduate School 'Molecular Cell Biology' MDC Cardiovascular and Metabolic Diseases and Affiliated Groups

CARDIO 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 **Cardiovascular and Metabolic Diseases research groups**. The MDC Cardio groups work in the fields of Heart Disease, Hypertension Vascular Disease and Kidney Disease and Metabolic Diseases, Genetics, Genomics and Bioinformatics.

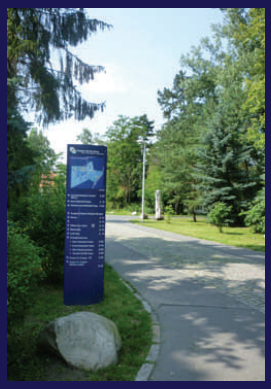
Please see the last page of this brochure for contact details of the PhD Programme coordinators.

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
- Skills Training and Development Activities including scientific lecture series and seminars, soft skills, symposia and PhD retreats, career development, German classes etc.
- 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 Campus

MDC Cardiovascular and Metabolic Diseases Groups

Molecular Biology of Peptide Hormones

Michael Bader

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The group is interested in the molecular biology and function of hormone systems involved in cardiovascular regulation. Besides the cloning and characterization of genes for the components, the physiological functions of the systems are analyzed by the production and analysis of transgenic and gene-targeted animal models.

Research interest:

- Molecular biology of genes coding for cardiovascular hormones
- Generation and characterization of genetically altered animal models for the functional analysis of cardiovascular hormones
- Development of transgenic technology in mouse and rat.

Publications:

Alenina N, Kikic D, Todiras M, Mosienko V, Qadri F, Plehm R, Boye P, Vil'ianovich L, Sohr R, Tenner K, Hörtnagl H, Bader M. (2009) Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc Natl Acad Sci USA. 106: 10332-10337

Shmidt T, Hampich F, Ridders M, Schultrich S, Hans VH, Tenner K, Vil'ianovich L, Qadri F, Alenina N, Hartmann E, Köhler M, Bader M. (2007) Normal brain development in importin α5 deficient mice. Nat Cell Biol. 9: 1337-1338.

Langenickel T, Buttgereit J, Pagel-Langenickel I, Lindner M, Beuerlein K, Al-Saadi N, Plehm R, Popova E, Tank J, Dietz R, Willenbrock R, Bader M. (2006) Cardiac hypertrophy in transgenic rats expressing a dominant negative mutant of the natriuretic peptide receptor B. Proc Natl Acad Sci USA 103: 4735-4740

Walther D, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, Bader M. (2003). Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science299, 76

Walther DJ, Peter JU, Winter S, Höltje M, Paulmann N, Grohmann M, Vowinckel J, Alamo-Bethencourt V, Wilhelm CS, Ahnert-Hilger G, Bader M. (2003). Serotonylation of small GTPases is a signal transduction pathway that triggers platelet α-granule release. Cell, 115, 851-862.

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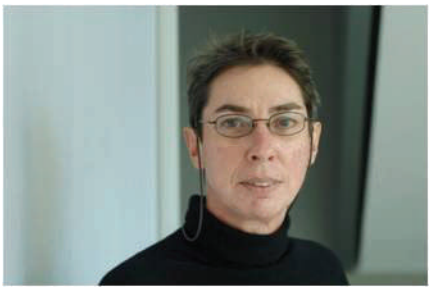
Signal Transduction/ Developmental Biology



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We analyze the functions of signaling molecules and of transcription factors in development of the nervous system and muscle. For this work, we use mice as a model organism. The molecular genetics of mice is well developed, and homologous recombination combined with embryonic stem cell technology can be used to introduce deletions or insertions into the genome. A further development of the technique, the Cre/LoxP technology, allows us now to introduce conditional mutations that are restricted to a particular cell lineage. We have used these technologies to analyze signals that maintain muscle progenitor cells and that allow the formation of satellite cells, the stem cells of the adult muscle. In addition, we identified the function of several transcription factors in development of the nervous system. Among these is a novel factor, Insm1,that we found unexpectedly to perform also important functions in development of pancreatic beta-cells, the insulin-producing endocrine cells.

Publications:

Sieber MA, Storm R, Martinez-de-la-Torre M, Muller T, Wende H, Reuter K, Vasyutina E, Birchmeier C. Lbx1 acts as a selector gene in the fate determination of somatosensory and viscerosensory relay neurons in the hindbrain. J Neurosci. 2007 May 2;27(18):4902-9.

Vasyutina E, Lenhard DC, Wende H, Erdmann B, Epstein JA, Birchmeier C. RBP-J (Rbpsuh) is essential to maintain muscle progenitor cells and to generate satellite cells. Proc Natl Acad Sci U S A. 2007 Mar 13;104(11):4443-8.

Willem M, Garratt AN, Novak B, Citron M, Kaufmann S, Rittger A, DeStrooper B, Saftig P, Birchmeier C, Haass C. Control of peripheral nerve myelination by the beta-secretase BACE1. Science. 2006 Oct 27;314(5799):664-6.

Gierl MS, Karoulias N, Wende H, Strehle M, Birchmeier C. The zinc-finger factor Insm1 (IA-1) is essential for the development of pancreatic beta cells and intestinal endocrine cells. Genes Dev. 2006 Sep 1;20(17):2465-78.

Wildner H, Muller T, Cho SH, Brohl D, Cepko CL, Guillemot F, Birchmeier C. dILA neurons in the dorsal spinal cord are the product of terminal and non-terminal asymmetric progenitor cell divisions, and require Mash1 for their development. Development. 2006 Jun;133(11):2105-13.

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Mol Neuro

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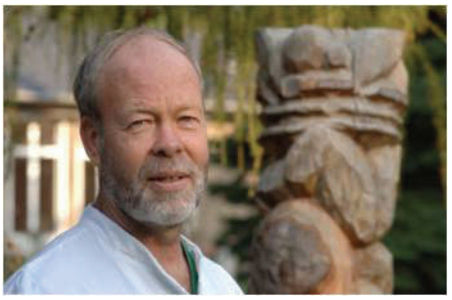
Clinical Cardiology



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The group is investigating molecular signalling pathways in heart failure development. In addition, sensitive methods for early detection of heart failure by cardiac MRI and electrophysiologic markers are developed in order to understand the pathophysiologic development and to gain the ability of testing new approaches in small patient numbers. With regard to signalling pathways, achievements were made with regard to the molecular control of cardiomyocyte apoptosis. In addition, contrast-enhanced cardiac MRI of patients with myocarditis, ischemic heart disease and dilated cardiomyopathy have revealed novel insight into heart failure development and distribution of injury sites. Genetic analysis of heart failure patients revealed new insights into the mechanisms of disease progression.

Publications:

Baurand A, Zelarayan L, Betney R, Gehrke C, Dunger S, Noack C, Busjahn A, Huelsken J, Taketo MM, Birchmeier W, Dietz R, Bergmann MW. (2007) Beta-catenin downregulation is required for adaptive cardiac remodeling. Circ Res 100, 1353-62.

Hauck L, Harms C, Grothe D, An J, Gertz K, Kronenberg G, Dietz R, Endres M, von Harsdorf R. (2007) Critical role for FoxO3adependent regulation of p21CIP1/WAF1 in response to statin signaling in cardiac myocytes. Circ Res; 100, 50-60.

Langenickel TH, Buttgereit J, Pagel-Langenickel I, Lindner M, Monti J, Beuerlein K, Al-Saadi N, Plehm R, Popova E, Tank J, Dietz R, Willenbrock R, Bader M. (2006) Cardiac hypertrophy in transgenic rats expressing a dominant-negative mutant of the natriuretic peptide receptor B. Proc Natl Acad Sci USA; 103, 4735-40.

von Harsdorf R, Poole-Wilson PA, Dietz R. (2004) Regenerative capacity of the myocardium: implications for treatment of heart failure. Lancet; 363, 1306-13.

Engel FB, Hauck L, Boehm M, Nabel EG, Dietz R, von Harsdorf R. (2003) p21(CIP1) Controls proliferating cell nuclear antigen level in adult cardiomyocytes. Mol Cell Biol; 23, 555-65.

Friedrich MG, Niendorf T, Schulz-Menger J, Gross CM, Dietz R. (2003) Blood oxygen level-dependent magnetic resonance imaging in patients with stress-induced angina. Circulation; 108, 2219-23.

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Neuromuscular and Cardiovascular Cell Biology

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Our long-term goal is to establish how mechanical input is translated into molecular signals. We focus on titin, the largest protein in the human body and the multifunctional coxsackie-adenovirus receptor (CAR). To lay the groundwork for the in vivo analysis of titin's multiple signaling, elastic, and adaptor domains, we have generated various titin deficient mice (knock-in and conditional knockout animals) and established a tissue culture system to study titin's muscle and non-muscle functions. We utilize a combination of cell-biological, biochemical, and genetic tools to establish titin as a stretch sensor converting mechanical into biochemical signals. Using a comparable loss of function approach we have created a conditional knock-out of the coxsackie-adenovirus receptor. With these mice, we have demonstrated that CAR is crucial for embryonic development and determines the electrical properties of the heart.

Publications:

Raddatz K, Albrecht D, Hochgräfe F, Hecker M, Gotthardt M. A proteome map of murine heart and skeletal muscle. Accepted in Protecomics 2-2008

Jansen P., Giehl K., Nyengaard J.R., Teng K., Lioubinski O., Sjoegaard S.S., Breiderhoff T., Gotthardt M., Lin F., Eilers A., Petersen C.M., Lewin G.R., Hempstead B.L., Willnow T.E., Nykjaer A. (2007) Roles for the pro-neurotrophin receptor sortilin in neuronal development, aging and brain injury. Nat Neurosci. 10(11):1449-57.

Granzier, H., Radke, M., Royal, J., Wu, Y., Irving, T.C., Gotthardt, M., Labeit, S. (2007) Genomic and functional analysis of avian, murine, and human titin supports splice diversity as an important mechanism for regulating biomechanics of striated muscle. Am J Physiol Regul Integr Comp Physiol 293: R557–R567

Radke, M., Peng, J., Wu, Y., McNabb, M., Nelson, O.L., Granzier, H., Gotthardt, M. (2007) Targeted deletion of Titin's N2B region leads to diastolic dysfunction and cardiac atrophy. Proc. Natl. Acad. Sci. USA. 104(9), 3444-3449

Peng J., Raddatz, K., Molkentin, J.D., Wu, Y., Labeit, S., Granzier, H., Gotthardt, M. (2007) Cardiac hypertrophy and reduced contractility in titin kinase deficient hearts. Circulation 13;115(6):743-5

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Clinical and Molecular Oncology

Research interest:

- Development of endocrine organs (thyroid, hypothalamus, pituitary, gonads).
- The impact of thyroid hormones and fetal/neonatal hypothyroidism on the development of the CNS.
- Clinical Endocrinology (thyroid disease, disorders of growth, puberty, and bone metabolism, sex-differentiation, and adrenogenital syndrome - AGS), newborn screening (hypothyroidism, AGS)

Annette Grüters

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Publications:

Alt B, Elsalini OA, Schrumpf P, Haufs N, Lawson ND, Schwabe GC, Mundlos S, Gruters A, Krude H, Rohr K (2006) Arteries defi ne the position of the thyroid gland during its developmental relocalisation. Development 133:3797-804

Biebermann H, Castaneda T, van Landeghem F, von Deimling A, Escher F, Brabant G, Hebebrand J, Hinney A, Tschöp M, Gruters A, Krude H (2006) A role for beta-melanocyte-stimulating hormone in human body-weight regulation. Cell Metab. 3:141-6

Biebermann H, Ambrugger P, Tarnow P, von Moers A, Schweizer U, Grueters A (2005) Extended clinical phenotype, endocrine investigations and functional studies of a loss-of-function mutation A150V in the thyroid hormone specifi c transporter MCT8. Eur J Endocrinol 153(3):359-66

Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, Kuiper GG, Balkassmi S, Uitterlinden AG, Koehrle J, Rodien P, Halestrap AP, Visser TJ (2004) Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 364:1435-7

Krude H, Biebermann H, Schnabel D, Tansek MZ, Theunissen P, Mullis PE, Grueters A (2003) Obesity due to proopiomelanocortin defi ciency: three new cases and treatment trials with thyroid hormone and ACTH4-10. J Clin Endocrinol Metab 88(10):4633-40

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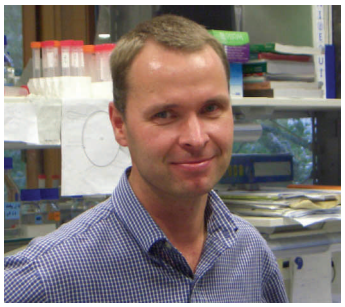
Membrane Biochemistry and Molecular Cell Biology



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Our group is active in the field of cellular and molecular neuroscience with the following major areas:

(1) Cellular and molecular mechanisms of synaptic vesicle recycling;

(2) Regulation of synaptic transmission and vesicle turnover by phosphoinositides;

(3) Molecular basis of the recognition of postsynaptic ion channels by endocytic adaptor;

(4) Proteins and cytoplasmic scaffolds and their role in synaptic plasticity;

(5) Ubiquitin-mediated modulation of synaptic morphogenesis and membrane turnover;

(6) Cellular and molecular mechanisms involved in the establishment and maintenance of;

(7) Neuronal polarity and its implications for axonal regeneration.

Publications:

Jung N, Wienisch M, Gu M, Rand JB, Müller SL, Krause G, Jorgensen EM, Klingauf J, Haucke V. (2007) Molecular basis of synaptic vesicle cargo recognition by the endocytic sorting adaptor stonin 2. J Cell Biol. Dec 31;179(7):1497-510.

Kastning K, Kukhtina V, Kittler JT, Chen G, Enders S, Lee SH, Sheng M, Yan Z, Haucke V (2007) Molecular determinants for the interaction between AMPA-type glutamate receptors and theclathrin adaptor complex AP-2. Proc Natl Acad Sci USA 104:2991-9

Diril MK, Wienisch M, Jung N, Klingauf J, Haucke V (2006) Stonin 2 is an AP-2-dependent endocytic sorting adaptor for synaptotagmin internalization. Dev Cell 10:233-44

Krauss M, Kukhtina V, Pechstein A, Haucke V (2006) Stimulation of PIPK type I-mediated phosphatidylinositol (4,5)-bisphosphate synthesis by endocytic AP-2mu adaptor cargo complexes.Proc Natl Acad Sci USA 103:11934-39

Jia JY, Lamer S, Schumann M, Krause E, Haucke V (2006) Quantitative proteomic analysis of detergent-resistant membranes from chemical synapses: evidence for cholesterol as spatial organizer of synaptic vesicle cycling. Mol Cell Proteomics 5:2060-71

Experimental Genetics of Cardiovascular Diseases

My research program is focussed on the identification of complex cardiovascular disorders. Our general approach is to dissect genetic networks systematically across biological scale, from molecular to physiology, using a reference population of recombinant inbred strains.

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Publications:

Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, de Silva U, Bailey SL, Witte T, Vyse TJ, Kere J, Pfeiffer C, Harvey S, Wong A, Koskenmies S, Hummel O, Rohde K, Schmidt RE, Dominiczak AF, Gahr M, Hollis T, Perrino FW, Lieberman J, Hubner N. (2007). Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nature Genetics 39: 1065-7.

Petretto, E., Mangion, J., Cook, S.A., M., Aitman, T.J., Kren, V., Pravenec, M., Schulz, H., Fischer, J. and N. Hubner. (2006). Response: Normalisation procedures and detection of linkage signal in genetical-genomics experiments. Nature Genetics 38: 9-10.

N. Hubner. (2006). Expressing physiology. Nature Genetics 38: 140-141.

Hubner, N., Wallace, C.A., Zimdahl, H., Petretto, E., Schulz, H., Maciver, F., Müller, M., Hummel, O., Monti, J., Zidek, V., Musilova, A., Kren, V., Causton, H., Game, L., Born, G., Schmidt, S., Müller, A., Cook, S.A., Kurtz, T.W., Whittaker, J., Pravenec, M. and T.J. Aitman. (2005). Integrated transcriptional profiling and linkage analysis for disease gene identification. Nature Genetics 37: 243-253.

Zimdahl, H., Nyakatura, G., Brandt, P., Schulz, H., Hummel, O., Fartmann, B., Brett, D., Droege, M., Monti, J., Lee, Y. A., Sun, Y. Y., Zhao, S. Y., Winter, E. E., Ponting, C. P., Chen, Y., Kasprzyk, A., Birney, E., Ganten, D, and Hübner, N. (2004). A SNP map of the rat genome generated from cDNA sequences. Science, 303, 807.

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Mobile DNA

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Transposons ("jumping genes") are discrete segments of DNA that have the distinctive ability to move and replicate within genomes across the tree of life. Transposons offer a new model to study DNA recombination in higher organism, as well as host-parasite interaction. Transposons are also natural gene delivery vehicles that are being developed as genetic tools. Our laboratory is following the strategy of understanding the mechanism of transposition and its regulation and translate this knowledge to derive transposon-based genetic tools for genome manipulation or for gene therapy.

Publications:

Sinzelle L; Izsvak Z; Ivics Z. Molecular domestication of transposable elements: From detrimental parasites to useful host genes. Cellular and Molecular Life Sciences 66 (6): 1073-1093 (2009-03)

Mates L; Chuah MK; Belay E; Jerchow B; Manoj N; Acosta-Sanchez A; Grzela DP; Schmitt A; Becker K; Matrai J; Ma L; Samara-Kuko E; Gysemans C; Pryputniewicz D; Miskey C; Fletcher B; Vandendriessche T; Ivics Z; Izsvak Z. Molecular evolution of a novel hyperactive Sleeping Beauty transposase enables robust stable gene transfer in vertebrates. Nature Genetics 41 (6): 753-761 (2009-06)

Xue X; Huang X; Nodland SE; Mates L; Ma L; Izsvak Z; Ivics Z; Lebien TW; McIvor RS; Wagner JE; Zhou X. Stable gene transfer and expression in cord blood-derived CD34+ hematopoietic stem and progenitor cells by a hyperactive Sleeping Beauty transposon system. Blood 114 (7): 1319-1330 (2009-08-13)

Orban TI; Apati A; Nemeth A; Varga N; Krizsik V; Schamberger A; Szebenyi K; Erdei Z; Varady G; Karaszi E; Homolya L; Nemet K; Gocza E; Miskey C; Mates L; Ivics Z; Izsvak Z; Sarkadi B. Applying a "double-feature" promoter to identify cardiomyocytes differentiated from human embryonic stem cells following transposon-based gene delivery. Stem Cells 27 (5): 1077-1087 (2009-02-20)

Izsvak Z; Chuah MK; Vandendriessche T; Ivics Z. Efficient stable gene transfer into human cells by Sleeping Beauty transposon vectors. Methods : (2009-07-14)

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Physiology, Pathology and Cell Biology of Ion Transport

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Ion transport processes play crucial roles in neuronal excitability and intracellular signal transduction, transport of salt, water, and other substances across epithelia, and the homeostasis of extracellular, cytosolic, and vesicular compartments. We focus on three gene families, namely CLC chloride channels and transporter, KCNQ (Kv7) potassium channels, and KCC K-Cl-cotransporters. Our investigations stretch from structure-function studies and biophysical analysis to cell biological aspects like endocytosis and to the physiological and systemic role of particular transport proteins. We have identified several human genetic diseases that are due to mutations in ion channels and have generated various knock-out mouse models. Their phenotypes yield important insights into the normal role of particular ion transporters and indicate candidate genes for human diseases. In accord with the broad importance of ion transport, these disorders include epilepsy and neurodegeneration, deafness, kidney stones, urinary protein loss, hypertension, and thick bones (ostepetrosis), among others. Our work bridges the gap between molecular studies and systems biology.

Publications:

Novarino G., Weinert S., Rickheit G., Jentsch T.J. (2010). Endosomal chloride-proton exchange rather than chloride conductance is crucial for renal endocytosis. Science 328, 1398-1401.

Weinert S., Jabs S., Supanchart C., Schweizer M., Gimber N., Richter M., Rademann J., Stauber T., Kornak U., Jentsch T.J. (2010). Lysosomal pathology and osteopetrosis upon loss of H+-driven lysosomal Cl- accumulation. Science 328,1401-1403.

Rickheit G., Maier H., Strenzke N., Andreescu C.E., De Zeeuw C.I., Zdebik A.A., Jentsch T.J. (2008). Endocochlear potential depends on chloride channels: mechanism underlying deafness in Bartter syndrome IV. EMBO J. 27, 2907-2917.

Lange P.F., Wartosch L., Jentsch T.J., Fuhrmann J.C. (2006). ClC-7 requires Ostm1 as a β-subunit to support bone resorption and lysosomal function. Nature 440, 220-223

Kharkovets T., Dedek K., Maier H., Schweizer M., Khimich D., Nouvian R., Vardanyan V., Leuwer R., Moser T., Jentsch T.J. (2006). Mice with altered KCNQ4 K+ channels implicate sensory outer hair cells in human progressive deafness. EMBO J. 25, 642-652.

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MolNeuro

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Angiogenesis and Cardiovascular Pathology

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Our goal is to generate novel genetic insights in the regulation of vascular development and vessel identity that can translate into therapeutic strategies.Our research projects aim at understanding the molecular regulation of angiogenesis and arteriogenesis. We focus on two crucial aspects:

1) differentiation and guidance of angiogenic vessel sprouts by endothelial tip cells (LeNoble, Nature 2004),

2) imprinting of arterial-venous identity in blood vessels by neural guidance genes and hemodynamic factors (LeNoble, Development 2004).

For this purpose we characterize the mechanisms of vascular development in experimental models including (transgenic) zebrafish, xenopus, chick and mouse embryo. In addition, the concepts emerging from understanding the basic molecular principles governing vascular growth are translated into relevant pathologic settings including cerebral and cardiac ischemia models, and cancer. We specifically address arterial collateral development upon arterial occlusion and prevention-recovery from target organ damage (heart infarct, stroke).

Publications:

Ahmad S, Hewett PW, Wang P, Al-Ani B, Cudmore M, Fujisawa T, Haigh JJ, le Noble F, Wang L, Mukhopadhyay D, Ahmed A (2006).. Direct evidence for endothelial vascular endothelial growth factor receptor-1 function in nitric oxide-mediated angiogenesis Circ Res. 99, 715-22.

Nguyen TH, Eichmann A, Le Noble F, Fleury V (2006). Dynamics of vascular branching morphogenesis: the effect of blood and tissue flow. Phys Rev E 73, 061907.

Eichmann A, Le Noble F, Autiero M, Carmeliet P (2005). Guidance of vascular and neural network formation. Curr Opin Neurobiol. 15,108-15.

le Noble F, Fleury V, Pries A, Corvol P, Eichmann A, Reneman RS (2005). Control of arterial branching morphogenesis in embryogenesis: go with the flow. Cardiovasc Res. 65, 619-28.

Lu X*, Le Noble F*, Yuan L*, Jiang Q, De Lafarge B, Sugiyama D, Breant C, Claes F, De Smet F, Thomas JL, Autiero M, Carmeliet P, Tessier-Lavigne M, Eichmann A (2004). The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system. Nature. 432, 179-86. *contributed equally

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Genetics of Allergic Disease

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The allergic diseases, particularly atopic dermatitis, food allergy, asthma, and hay fever, are among the most common chronic diseases in man. The prevalence of atopic diseases has increased to epidemic dimensions over the past decades. In the industrialized countries, 25-30% of the population are affected. A strong genetic component in atopy and has been recognized. Our group is using genetic and genomic approaches to identify genes and genetic variants that predispose to atopic dermatitis and atopy. The identification of the molecular pathways underlying allergic disease will provide novel targets for preclinical diagnosis, disease prevention, and therapeutic intervention.

Publications:

Schulz F, Marenholz I, Fölster-Holst R, Chen C, Sternjak A, Esparza-Gordillo J, Baumgrass R, Grüber C, Nickel R, Schreiber S, Stoll M, Rüschendorf F, Hubner N, Wahn U, Lee YA. A common haplotype of the interleukin-31 gene (IL31) influencing gene expression is associated with nonatopic eczema. J All Clin Immunol 2007 in press.

Soderhall, C, Marenholz, I, Kerscher, T, Gruber, C, Worm, M, Esparza-Gordillo, J, Ruschendorf, F, Rohde, K, Schulz, H, Wahn, U, Hubner, N, and Lee, YA. Variants in a novel epidermal collagen gene (COL29A1) are associated with atopic dermatitis. PLoS Biology 2007; 5:1952-1961.

Lee-Kirsch MA, Gong M#, Chowdhury D#, Senenko L#, Engel L#, Lee YA#, de Silva U, Bailey SL, Witte T, Vyse TJ, Kere J, Pfeiffer C, Harvey S, Wong A, Koskenmies S, Hummel O, Rohde K, Schmidt RE, Dominiczak AF, Gahr M, Hollis T, Perrino FW, Lieberman J, Hubner N. Mutations in the 3´-5´ DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nature Genet 2007; 39:1065-67. #joined second author.

Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, Gruber C, Lau S, Wahn U, and Lee YA. Filaggrin loss-of-function-mutations predispose to phenotypes involved in the atopic march. J All Clin Immunol 2006; 118:866-71.

Söderhäll C, Marenholz I, Nickel R, Grüber C, Kehrt R, Griffioen RW, Meglio P, Tarani L, Gustafsson D, Hoffmann U, Gerstner B, Müller S, Wahn U, Lee YA. Lack of association of the GPRA (G protein-coupled receptor for asthma susceptibility) gene with atopic dermatitis. J All Clin Immunol 2005;116(1):220-1.

HELMHOLTZ GRADUATE SCHOOL Molecular Cell Biology

Genetics, Nephrology, Hypertension, and Vascular Injury

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The Department of Nephrology/Hypertension/Clinical Pharmacology, headed by Friedrich C. Luft, encompasses several research groups (Jens Jordan, Clinical Research Center; Wolf-Hagen Schunck, Eicosanoids; Dominik N. Müller, Helmholtz Fellow; Kai Schmidt-Ott, Emmy Noether Fellow) that are reported elsewhere in the MDC Research Report. Friedrich C. Luft's group is interested in molecular and genetic mechanisms contributing to blood pressure regulation, cardiovascular, and renal diseases. Ralph Kettritz is pursuing mechanisms responsible for proteinase-3 (PR3) and myeloperoxidase (MPO) antibody-induced vasculitis. The neutrophil is the key cell in these diseases. He and his team recently showed that the major hisocompatibility complex HLA region largely explains genetic variance on PR3, that NB1 mediates surface expression of PR3, and that platelets can transfer receptors onto neutrophils.

Sylvia Bähring is pursuing the molecular genetics of autosomal-dominant brachydactyly and hypertension. She is elucidating a novel gene probably encoding for a micro-RNA. Volkmar Gross pursues blood pressure regulation and sympathetic nerve activity in several gene-deleted mouse models, and thereby utilizes state-of-the-art physiological techniques adapted to the 25 g conscious mouse. Anette Fiebeler uncovered hitherto fore unknown glucocorticoidmediated signaling via the mineralocorticoid receptor in vascular cells.

Publications:

Dragun, D., D. N. Muller, J. H. Brasen, L. Fritsche, M. Nieminen-Kelha, R. Dechend, U. Kintscher, B. Rudolph, J. Hoebeke, D. Eckert, I. Mazak, R. Plehm, C. Schonemann, T. Unger, K. Budde, H. H. Neumayer, F. C. Luft, and G. Wallukat, (2005), Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection: New England Journal of Medicine, v. 352, p. 558-569.

Radermacher, J., M. Mengel, S. Ellis, S. Stuht, M. Hiss, A. Schwarz, U. Eisenberger, M. Burg, F. C. Luft, W. Gwinner, and H. Haller, (2003), The renal arterial resistance index and renal allograft survival: New England Journal of Medicine, v. 349, p. 115-124.

Schmitt, R., W. Weichert, W. Schneider, F. C. Luft, and R. Kettritz, (2005), Pseudo-pseudo Meigs' syndrome: Lancet, v. 366, p. 1672-1672.

Engeli, S., Böhnke, J., Gorzelniak, K., Janke, J., Schling, P., Bader, M., Luft, F. C., and Sharma, A. M. (2005). Weight loss and the renin-angiotensin-aldosterone system. Hypertension, 45, 356-362.

Schroeder, C., S. Vernino, A. L. Birkenfeld, J. Tank, K. Heusser, A. Lipp, T. Benter, C. Lindschau, R. Kettritz, F. C. Luft, and J. Jordan, (2005), Plasma exchange for primary autoimmune autonomic failure: New England Journal of Medicine, v. 353, p. 1585-1590.

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Molecular Muscle Physiology

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Contractility of cardiac and smooth muscle is regulated by Ca2+, which enter the cells through voltage-gated L-type Ca2+ channels and subsequently induce the release of high amounts of Ca2+ from the sarcoplasmic reticulum into the myoplasm through calcium release channels. Ca2+ regulate both intracellular signalling pathways and contraction of the myofibrils. In cardiomyocytes, Ca2+ activate the myofibrils by binding to troponin C molecules, which turn the thin filament "on", allowing the molecular motor myosin to interact with the actin filament to produce force and shortening. In smooth muscle cells Ca2+ form a complex with calmodulin which activate the myosin light chain kinase, an enzyme which phosphorylates a 20kDa regulatory light chain of myosin, thus allowing the smooth muscle myosins to generate contraction upon interaction with the actin filaments. Likewise, the Ca2+/calmodulin complex regulates muscle cell growth by activation of calcineurin, which dephosphorylates the transcription factor NFAT3. Dephosphorylated NFAT3 translocates into the nucleus and increases transcription rate of hypertrophic genes. Because of their key-roles in muscle, we are studying the expression regulation, post-translational modifications, and functional roles of the subunits of L-type Ca2+ channel, proteins of the Ca2+ signalling pathways, and type II myosin in cardiac and smooth muscle. Any changes in these key proteins, by mutation, differential gene expression, alternative splicing of the transcripts, or post-translational modification modulate cardiac and smooth muscle function. Understanding muscle contraction regulation at the molecular and functional level provides an opportunity to develop new therapies for the treatment of cardiac and smooth muscle dysfunction.

Publications:

Lamounier-Zepter V; Look C; Alvarez J; Christ T; Ravens U; Schunck WH; Ehrhart-Bornstein M; Bornstein SR; Morano I. Adipocyte fatty acid-binding protein suppresses cardiomyocyte contraction. A new link between obesity and heart disease. Circulation Research 105 (4): 326-334 (2009-08-14)

Look C; Morano I; Lamounier-Zepter V. Human adipocyte-derived factors directly inhibit cardiac contraction. Journal of Muscle Research and Cell Motility 29 (6-8): 181-184 (2009)

Karczewski P; Haase H; Hempel P; Bimmler M. Agonistic antibody to the alpha(1)-adrenergic receptor mobilizes intracellular calcium and induces phosphorylation of a cardiac 15-kDa protein. Molecular and Cellular Biochemistry : (2009-08-15)

Panek AN; Posch MG; Alenina N; Ghadge SK; Erdmann B; Popova E; Perrot A; Geier C; Dietz R; Morano I; Bader M; Oezcelik C. Connective tissue growth factor overexpression in cardiomyocytes promotes cardiac hypertrophy and protection against pressure overload. PLoS ONE 4 (8): e6743 (2009)

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Experimental Ultrahigh-Field MR

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Our group is part of the recently inaugurated Ultrahigh-Field MR Facility at the Max-Delbrueck-Center for Molecular Medicine (MDC), Berlin, Germany. The group's Research concentrates on the development of MR-methodology and MR technology with a focus on new ways of mapping and probing morphology, function, physiology and metabolism together with explorations of the benefits and challenges of ultrahigh-field imaging to advance cardiovascular, neurovascular, molecular and other MRI applications. These efforts are designed to spatially resolve and characterize (patho)physiological processes and biophysical mechanisms to promote a transfer from basic research to (pre)clinical studies and vice versa. However, signal-to-noise ratio (SNR) and imaging speed have become an increasingly stringent limit in new MRI applications. Promising in this regard is the increase in magnetic field strengths available. Hence our group is very pleased to make access to state-of-the-art MR instruments dedicated to research available including access to a family of a multiple transmit 7.0 Tesla, a 3.0 Tesla and a 1.5 T whole body system (in collaboration with the Helios Clinic, Berlin), all equipped with 32 receive channel, and an 9.4 T animal MR system (Bruker Biospin). Acces to highresolution vertical bore NMR spectrometer (300 MHz, 400 MHz, 600 and 900 MHz, in collaboration with the Leibniz Institute for Molecular Pharmacology) is also available. Opportunities exist to collaborate with scientists at the Charite' - Universitätsmedizin Berlin, the National Metrology Institute (PTB) Berlin, the Leibniz-Institute for Molecular Pharmacology (FMP) Berlin, the Humboldt-University Berlin and at the Technical University of Berlin.

Publications:

T. Frauenrath, F. Hezel, U. Heinrichs, S. Kozerke, J. F. Utting, M. Kob, C. Butenweg, P. Boesiger, T. Niendorf. Feasibility of Cardiac Gating Free of Interference with Electro-Magnetic Fields. at 1.5 Tesla, 3.0 Tesla and 7.0 Tesla Using an MR-Stethoscope

Invest. Radiol., 44:539-47 (2009). J.F. Utting, S. Kozerke, R. Luechinger, R. Schnitker, R. Vohn, T. Niendorf. Feasibility of k-t BLAST for BOLD fMRI with a Spin-Echo Based Acquisition at 3.0 T and 7.0 T. Invest. Radiol., 44:495-502 (2009)

U. Heinrichs, J. F. Utting, T. Frauenrath, F. Hezel, G. A. Krombach, M. A. J. Hodenius, S. Kozerke, T. Niendorf. Myocardial T2* Mapping Free of Distortion Using Susceptibility Weighted Fast Spin-Echo Imaging: A Feasibility Study at 1.5 T and 3.0 T. Magn. Reson. Med., 62:822-828 (2009)

T. Niendorf, D.K. Sodickson. Parallel Imaging in Cardiovascular MRI: Methods and Applications. NMR Biomed. 19:325-41 (2006)

MicroRNA and Molecular Mechanisms of Metabolic Diseases

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MicroRNAs (miRNAs) are regulators of gene expression that control many biological processes in development, differentiation, growth and metabolism. Their expression levels, small size, abundance of repetitive copies in the genome and mode of action pose unique challenges in studies elucidating the function of miRNAs. New technologies for identification, expression profiling and target gene validation, as well as manipulation of miRNA expression in vivo, will facilitate the study of their contribution to biological processes and disease. Such information will be crucial to exploit the emerging knowledge of miRNAs for the development of new human therapeutic applications.

Publications:

Yi, R., Poy, MN., Stoffel, M., and Fuchs, E. (2008) A skin microRNA promotes differentiation by repressing 'stemness'. Nature. (In press).

Krek, A.*, Grun, D.*, Poy, MN.*, Wolf, R., Rosenberg, L., Epstein, EJ., MacMenamin, P., da Piedade, I., Gunsalus, KC., Stoffel, M., Rajewsky, N. (2005) Combinatorial microRNA target predictions. Nat. Genet. 37, 495-500. (* equal contribution)

Wolfrum, C., Poy, MN., and Stoffel, M. (2005) Apolipoprotein M is required for preβ-HDL formation, reverse cholesterol transport and protects against atherosclerosis. Nat. Med. 11, 418-22.

Poy, MN., Eliasson, L., Krützfeldt, J., Kuwajima, S, Ma, X., MacDonald, PE., Pfeffer, S., Tuschl, T., Rajewsky, N., Rorsman, P. and Stoffel, M. (2004) A pancreatic islet-specific microRNA regulates insulin secretion. Nature. 432, 226-30.

Poy, MN., Yang, Y., Rezaei, K., Fernstrom, MA., Lee, A.D., Kido, Y., Erickson, S., and Najjar, SM. (2002) CEACAM1 regulates insulin clearance in liver. Nat Genet. 30, 270-6.

HELMHOLTZ GRADUATE SCHOOL Molecular Cell Biology

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Circulatory physiology and microcirculation

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Research interest – microcirculation, blood rheology, vascular adaptation, angiogenesis, ischemia/reperfusion, endothelial surfaces with experiments and mathematical model simulations. 125 peer reviewed publications and 63 invited lectures since 1980.

In the past 5 years I have trained 30 graduate students.

Publications:

H.A.J. Struijker-Boudier, A.E. Rosei, P. Bruneval, P.G. Camici, F. Christ, D. Henrion, B.I. Lévy, A.R. Pries, J.-L. Vanoverschelde (2007) Evaluation of the microcirculation in hypertension and cardiovascular disease. Eur. Heart J. 28: 2834-2840

O. Hudlicka, M.D. Brown, S. May, A. Zakrzewicz, A.R. Pries (2006) Changes in capillary shear stress in skeletal muscles exposed to long-term activity: role of nitric oxide. Microcirculation 13: 249-259

A.R. Pries, T.W. Secomb (2005) Microvascular blood viscosity in vivo and the endothelial surface layer. Am. J. Physiol. 289: H2657-H2664

A.R. Pries, B. Reglin, T.W. Secomb (2005) Remodeling of blood vessels: Responses of diameter and wall thickness to hemodynamic and metabolic stimuli. Hypertension 46: 725-731

F. Le Noble, V. Fleury, A.R. Pries, P. Corvol, A. Eichmann, R.S. Reneman (2005) Control of arterial branching morphogenesis in embryogenesis: go with the flow. Cardiovasc. Res. 65: 619-628

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Systems Biology of Gene Regulatory Elements

The Rajewsky Lab uses computational and experimental methods to dissect, systems-wide, function and evolution of gene regulation in metazoans. One major focus is to understand more about gene regulation by small RNAs, in particular microRNAs. To probe general mechanisms in gene regulation of microRNAs, the lab works with cell lines. We are also investigating the function of small RNAs during very early development of C. elegans. Furthermore, the lab has established planaria as a model system within the lab. These freshwater flatworms are famous for their almost unlimited ability to regenerate any tissue via pluripotent, adult stem cells. The lab is studying the role of small RNAs in planarian regeneration.

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Publications:

Chen K; Maaskola J; Siegal ML; Rajewsky N. Reexamining microRNA site accessibility in Drosophila: a population genomics study. PLoS ONE 4 (5): e5681 (2009)

Stoeckius M; Maaskola J; Colombo T; Rahn HP; Friedlaender MR; Li N; Chen W; Piano F; Rajewsky N. Large-scale sorting of C. elegans embryos reveals the dynamics of small RNA expression. Nature Methods 6 (10): 745-751 (2009 -10)

Friedlaender MR; Adamidi C; Han T; Lebedeva S; Isenbarger TA; Hirst M; Marra M; Nusbaum C; Lee WL; Jenkin JC; Alvarado AS; Kim JK; Rajewsky N. High-resolution profiling and discovery of planarian small RNAs. Proceedings of the National Academy of Sciences of the United States of America 106 (28): 11546-11551 (2009-07-14)

Koralov SB; Muljo SA; Galler GR; Krek A; Chakraborty T; Kanellopoulou C; Jensen K; Cobb BS; Merkenschlager M; Rajewsky N; Rajewsky K. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. Cell 132 (5): 860-874 (2008-03-07)

Ender C; Krek A; Friedlaender MR; Beitzinger M; Weinmann L; Chen W; Pfeffer S; Rajewsky N; Meister G. A human snoRNA with microRNA-like functions. Molecular Cell 32 (4): 519-528 (2008-11-21)

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Molecular Pharmacology

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signaltransduction.html

Walter Rosenthal was appointed Scientific Director of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch in January 2009. The institute belongs to the Helmholtz Association of National Research Centers. Walter Rosenthal studied medicine at the Justus-Liebig-Universität Gießen, Germany, and at the Royal Free Hospital, School of Medicine in London, United Kingdom. In 1990, he became Assistant Professor (Habilitation) at the Free University of Berlin, Germany, carrying out studies on G-proteins, followed by two years as Visiting Professor and Heisenberg Fellow at Baylor College of Medicine, Houston, Texas, USA. From 1993 – 1996, he was the Director of the Rudolf-Buchheim-Institut for Pharmacology at the University of Gießen. In 1996, he became the Director of the Leibniz-Institut für Molekulare Pharmakologie (FMP) and, in 2000, was responsible for moving the FMP to the Berlin-Buch Campus in order to work more closely with the MDC. He is also a professor at the Charité – Universitätsmedizin Berlin, one of the largest university hospitals in Germany.

Publications:

Schmidt, A., Wiesner, B., Weisshart, K., Schulz, K., Furkert, J., Lamprecht, B., Rosenthal, W., & Schülein, R. (2009) Use of kaede fusions to visualize recycling of g protein-coupled receptors. Traffic 10: 2-15.

Lygren B, Carlson CR, Santamaria K, Lissandron V, McSorley T, Lorenz D, Wiesner B, Rosenthal W, Zaccolo M, Taskèn K, Klussmann E (2007) AKAP-complex regulates Ca2+ re-uptake into heart sarcoplasmic reticulum. EMBO Rep. 8: 1061-1067.

Stefan E, Wiesner B, Baillie GS, Mollajew R, Henn V, Lorenz D, Furkert J, Santamaria K, Nedvetsky P, Hundrucker C, Beyermann M, Krause E, Pohl P, Gall I, MacIntyre AN, Bachmann S, Houslay MD, Rosenthal W, Klussmann E (2007) Compartmentalization of cAMP-dependent signalling by phosphodiesterase-4D is involved in the regulation of Vasopressin-mediated water reabsorption in renal principal cells. J Am Soc Nephrol 18: 100-212.

Grantcharova E, Reusch HP, Grossmann S, Eichhorst J, Krell HW, Beyermann M, Rosenthal W, Oksche A (2006) N-terminal proteolysis of the ETB receptor abolishes its ability to induce EGF Receptor transactivation and contractile protein expression in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 26: 1288-1296.

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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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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)

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)

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)

Oeckinghaus A; Wegener E; Welteke V; Ferch U; Arslan SC; Ruland J; Scheidereit C; Krappmann D. Malt1 ubiquitination triggers NF-kappaB signaling upon T-cell activation. EMBO Journal 26 (22): 4634-4645 (2007-11-14)

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Molecular Cell Biology and Gene Therapy

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The kidney is a central organ in cardiovascular diseases and regulates volume and solute homeostasis in the body. The kidney is composed of structural units called nephrons, which consist of several different types of renal epithelial cells that facilitate directional transport.

Our group studies the molecular mechanisms of nephron morphogenesis and the maintenance of epithelial integrity later in life. We focus on transcription factors and their regulation of aspects of epithelial differentiation. We use mouse models and epithelial cell culture systems and employ a wide spectrum of techniques, including genome- wide gene expression analysis, DNA-protein interaction analysis as well as organ culture techniques of the developing kidney.

Publications:

Li JY, Paragas N, Ned RM, Qiu A, Viltard M, Leete T, Drexler IR, Chen X, Sanna-Cherchi S, Mohammed F, Williams D, Lin CS, Schmidt-Ott KM, Andrews NC, Barasch J. (2009) Scara5 is a ferritin receptor mediating non-transferrin iron delivery. Dev Cell. 16:35-46.

Schmidt-Ott KM, Barasch J. (2008) WNT/beta-catenin signaling in nephron progenitors and their epithelial progeny. Kidney Int. 74:1004-8.

Schmidt-Ott K.M., Masckauchan T.N., Chen X., Hirsh B.J., Sarkar A., Yang J., Paragas N., Wallace V.A., Dufort D., Pavlidis P., Jagla B., Kitajewski J., Barasch J. (2007) β-Catenin/TCF/Lef Controls A Differentiation-Associated Transcriptional Program In Renal Epithelial Progenitors. Development. 134(17):3177-90.

Schmidt-Ott, K.M., Mori, K., Li, J.Y., Kalandadze, A., Cohen, D.J., Devarajan, P., Barasch, J. (2007) Dual action of neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol. 18, 407-13.

Schmidt-Ott, K.M., Chen, X., Paragas, N., Levinson, R.S., Mendelsohn, C.L., Barasch,, J. (2006) c-kit delineates a distinct domain of progenitors in the developing kidney. Dev Biol. 299, 238-49.

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Intracellular Signalling and Mass Spectrometry

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Cells receive many different stimuli from their environment that influence their metabolism, interaction with other cells, proliferation, survival and other cellular processes involved in homeostasis and health of the organism. The signals from different external stimuli are integrated by signal transduction cascades that involve a multitude of proteins. While we know a lot about the function of individual proteins there is little information about the system as a whole. One of the greatest challenges today is to explore signaling among all cellular proteins in parallel. Recent developments in mass spectrometry have dramatically improved the analytical power of this technology. We are using mass spectrometry -based quantitative proteomics to investigate intracellular signaling on a global scale.

Publications:

Moese S, Selbach M, Brinkmann V, Karlas A, Haimovich B, Backert S, Meyer TF. (2007) The Helicobacter pylori CagA protein disrupts matrix adhesion of gastric epithelial cells by dephosphorylation of vinculin. Cell Microbiol., 9, 1148-1161.

Selbach M, Mann M. (2006) Protein interaction screening by quantitative immunoprecipitation combined with knockdown (QUICK). Nature Methods,3, 981-983

Becker, D., Selbach, M., Rollenhagen, C., Ballmaier, M., Meyer, T.F., Mann, M. and Bumann, D. (2006) Robust Salmonella metabolism limits possibilities for new antimicrobials. Nature, 440, 303-307. (shared first authorship)

Backert, S., and Selbach, M. (2005) Tyrosine-phosphorylated bacterial effector proteins: the enemies within. Trends Microbiol., 13, 476-484.

Selbach, M., Moese, S., Hurwitz, R., Hauck, C.R., Meyer, T.F. and Backert, S. (2003) The Helicobacter pylori CagA protein induces cortactin dephosphorylation and actin rearrangement by c-Src inactivation. EMBO J., 22, 515-528.

HELMHOLTZ GRADUATE SCHOOL Molecular Cell Biology

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Epithelial Polarity and Zebrafish Genetics

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cellpolarity/

Vertebrate organs are derived from epithelial sheets of cells that undergo complex morphogenetic transformations. I am interested in the development of the zebrafish heart, a relatively simple organ compared with its mammalian counterpart, to better understand the genetic control of organ morphogenesis. Insights from developmental genetics and cell biology deployed within my research group will be used in collaboration with clinical researchers to identify genes responsible for human congenital heart disease.

I have a strong interest in helping to establish the "TransCard" program. I believe that an interdisciplinary curriculum is essential for preparing the next generation of researchers to work in the field of translational medicine. My training expertise is in the fields of developmental genetics and cell biology.

Publications:

Seipold, S, Priller,F, Goldsmith,P, Harris,B, Baier,H, and Abdelilah-Seyfried,S. (2009). Non-SMC condensin I complex proteins control chromosome segregation and survival of proliferating cells in the zebrafish neural retina. BMC Dev. Biol., 9, 40.

Nyholm,KM, Abdelilah-Seyfried,S, and Grinblat,Y. (2009). A novel genetic mechanism regulates dorsolateral hinge point formation during zebrafish cranial neurulation. J. Cell Sci., 122, 2137-2148.

Hava, D, Förster, U, Matsuda, M, Chitnis, A, Link, B, and Abdelilah-Seyfried, S. (2009). Apical membrane maturation and cellular rosette formation during morphogenesis of the zebrafish lateral line. J. Cell Sci., 122, 687-695.

Bakkers,J, Verhoeven,M, and Abdelilah-Seyfried,S. (2009). Shaping the zebrafish heart: from left-right axis specification to epithelial tissue morphogenesis. Dev. Biol., 330, 213-220.

Lange M; Kaynak B; Forster UB; Toenjes M; Fischer JJ; Grimm C; Schlesinger J; Just S; Dunkel I; Krueger T; Mebus S; Lehrach H; Lurz R; Gobom J; Rottbauer W; Abdelilah-Seyfried S; Sperling S. (2008) Regulation of muscle development by DPF3, a novel histone acetylation and methylation reader of the BAF chromatin remodeling complex. Genes & Development 22 (17): 2370-2384

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Molecular and Cellular Basis of Embryonic Development

Research interest:

Mechanisms controlling regional specification of the anterior endoderm, early development of the pancreas in vertebrates, role of post-transcriptional mechanisms in pancreatic development, stem cell analysis to define lineage-specific differentiation towards endodermal tissues, including hepatic and pancreatic lineages.

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Publications:

Francesca M. Spagnoli, Rosa*, A, Ali H. Brivanlou (2009). Mesendodermal lineage specification in embryonic stem cells is under the control of a conserved microRNA family. Developmental Cell 16, 517-27. *co-first authors

Francesca M. Spagnoli and Ali H. Brivanlou (2008). The Gata5 target, TGIF2, defines the pancreatic region by modulating BMP signals within the endoderm, Development, 135, 451-461.

Francesca M. Spagnoli (2007). From endoderm to pancreas: a multistep journey. The CMLS Journal 64, 2378-2390.

Gopal Sapkota, Claudio Alarcón, Francesca M. Spagnoli, Ali H. Brivanlou and Joan Massagué (2007). Balancing BMP signaling through integrated inputs into the Smad1 linker, Molecular Cell, 25, 441–454.

Francesca M. Spagnoli and Ali H. Brivanlou (2006). The RNA Binding Protein, Vg1RBP, is Required for Pancreatic Fate Specification, Developmental Biology, 292, 442-456.

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Cell Polarity and Epithelial Development

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The major focus of our research group lies on the elucidation of genetic factors contributing to heart failure and sudden cardiac death. The various forms of cardiomyopathies (hypertrophic, dilated and arrhythmogenic right ventricular cardiomyopathy, left ventricular noncompaction) serve as human model diseases whereas mouse and zebrafish models are used or, respectively, generated to pinpoint molecular pathways. Over the last five to ten years, many disease causing mutations contributing to genetic forms of heart failure in humans have been identified. The challenge of the coming years will be to delineate the pathophysiology of these mutations in detail. Important extensions of our research program are experiments through which we try to understand the regenerative capacity of the heart. And, finally, we aim to shed light on the role of nuclear receptors on cardiac metabolism and gene expression in the genesis of heart failure. Eventually, a better understanding of the pathophysiology of these model diseases will enable us to find better ways of diagnosing and treating our heart failure patients.

Publications:

MacRae, C. A., Birchmeier, W., and Thierfelder, L. (2006). Arrhythmogenic right ventricular cardiomyopathy: moving toward mechanism. Journal of Clinical Investigation, 116, 1825-1828.

Heuser A, Plovie ER, Ellinor PT, Grossmann KS, Shin JT, Wichter T, Basson CT, Lerman BB, Sasse-Klaassen S, Thierfelder L, MacRae CA, Gerull B. (2006) Mutant desmocollin-2 causes arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 79, 1081-8

Ellinor PT, Sasse-Klaassen S, Probst S, Gerull B, Shin JT, Toeppel A, Heuser A, Michely B, Yoerger DM, Song BS, Pilz B, Krings G, Coplin B, Lange PE, Dec W, Hennies HC, Thierfelder L, MacRae CA. (2006) A Novel Locus for Dilated Cardiomyopathy, Diffuse Myocardial Fibrosis, and Sudden Death on Chromosome 10q25-26. J Am Coll Cardiol. 48, 106-11

Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, Thierfelder L, Stuckless SN, Dicks EL, McKenna WJ, Connors SP. (2005) The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol., 45, 400-8.

Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, Lerman BB, Markowitz SM, Ellinor PT, MacRae CA, Peters S, Grossmann KS, Drenckhahn J, Michely B, Sasse-Klaassen S, Birchmeier W, Dietz R, Breithardt G, Schulze-Bahr E, Thierfelder L. (2004) Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet.; 36,1162-4. Erratum in:Nat Genet. (2005);37:106.

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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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Molecular Cardiovascular Research

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We aim at functional characterization of orphan endocytic receptors of the LDL receptor and Sortilin gene families, focusing on their roles in the cardiovascular and nervous system. Following a concept of molecular physiology we apply transgene technologies to generate model organisms with altered receptor expression (e.g., gene inactivation, transgene overexpression) and to study the consequences for organ function in vivo. Leads from animal experimentation are followed up by biochemical and cell biological studies to unravel the underlying molecular mechanisms of receptor activity.

Publications:

Jansen, P., Giehl, K., Nyengaard, J.R., Teng, K., Lioubinski, O., Sjoegaard, S.S., Breiderhoff, T., Gotthardt, M., Lin, F., Eilers, A., Petersen, C.M., Lewin, G.R., Hempstead, B.L., Willnow, T.E*. and A. Nykjaer*. (2007) Distinct apoptotic roles for sortilin in neuronal development, ageing, and brain injury. Nat. Neurosci. 10(11), 1449-1457. * joined corresponding authors

Rogaeva, E., Meng, Y., Lee, J.H., Gu,Y., Kawarai, T., Zou, F., Katayama,T., Baldwin, C.T., Cheng, R., Hasegawa, H., Chen, F., Shibata, N., Lunetta, K.L., Pardossi-Piquard, R., Bohm, C., Wakutani, Y., Cupples, L.A., Cuenco, K.T., Green, R.C., Pinessi, L., Rainero, I., Sorbi, S., Bruni, A., Duara, R., Friedland, R.P., Inzelberg,R., Hampe, W., Bujo, H., Song, Y.Q., Andersen, O.M., Willnow, T.E., Graff-Radford, N., Petersen, R., Dickson, D., Der, S.D., Fraser, P.E., Schmitt-Ulms, G., Younkin, S., Mayeux, R., Farrer, L.A., and P. St George-Hyslop. (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer's Disease. Nat. Genet. 39: 168-177.

Hammes, A., Andreassen, T. K., Spoelgen, R., Raila, J., Huebner, N., Schulz, H., Metzger, J., Schweigert, F. J., Luppa, P. B., Nykjaerr, A. and T. E. Willnow. (2005) Impaired development of the reproductive organs in mice lacking megalin, an endocytic receptor for steroid hormones. Cell 122: 751-762.

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Mathematical Modelling of Cellular Processes

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Complex diseases are often characterised by an accumulation of multiple perturbations in rather large and complex cellular networks. The consequences of these perturbations, such as mutations or over-expression of proteins, can hardly be analysed by pure reasoning. Here, mathematical modelling contributes to a deeper understanding of the regulatory systems and provides thus a better basis for the interpretation of high-throughput data and identification of effective drug targets.

Our group develops and analyses mathematical models of signalling pathways and gene-regulatory networks in normal and disease states. For our investigations we use tools such as simulations, bifurcation analyses and sensitivity analyses. These give insights into the dynamical properties of the systems and help to identify most sensitive processes and critical regulations. Another important aspect is the investigation of cell specific differences in signalling and gene-regulatory networks since these are critically involved in the prediction of the efficiency and possible side-effects of drugs.

So far we use qualitative and quantitative dynamic modelling depending on the available experimental data. In the next future we also plan to apply logical modelling approaches which allow the description of large interaction maps with only minor knowledge about kinetic data (collaboration with Steffen Klamt, Magdeburg).

Publications:

J. Wolf, S. Dronov, F. Tobin & I. Goryanin (2007), The impact of the regulatory design on the response of EGFR-mediated signal transduction towards oncogenic mutations. FEBS Journal 274 (21), 5505-5517.

J. Wolf, S. Becker-Weimann & R. Heinrich (2005), Analysing the robustness of cellular rhythms, IEE Syst. Biol. 2(1), 35 -41.

S. Becker-Weimann, J. Wolf, H. Herzel & A. Kramer (2004), Modeling feedback loops of the mammalian circadian oscillator. Biophysical Journal 87, 3023-3034.

J. Wolf, H. Sohn, R. Heinrich & H. Kuriyama (2001), Mathematical analysis of a mechanism for autonomous metabolic oscillations in continuous culture of Saccharomyces cerevisiae. FEBS Letters 499, 230-234.

J. Wolf & R. Heinrich (2000), The effect of cellular interaction on glycolytic oscillations in yeast. A theoretical investigation. Biochemical Journal 345, 321-334.

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