



Department of Developmental Genetics

(Established: 11/2003)

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Introduction

The major focus of the Department of Developmental Genetics is on understanding the regulatory networks controlling tissue formation and organogenesis during embryonic development. We investigate patterning, induction and differentiation processes in the trunk. Tightly linked to this major goal is the molecular analysis of tumour formation. In recent years it has become apparent that tumours can develop from cancer stem cells triggering aberrant tissue formation. Cancer stem cells derive from adult stem cells required for tissue regeneration in the adult organism, and follow the principles of embryonic development. Thus, processes of embryonic development, tissue regeneration and cancer are closely related. There is also compelling evidence that tumour spreading to other sites in the body also requires genetic programs regulating cellular shape changes, which are shared between embryos and tumours. This switch in cellular behaviour, called epithelial-mesenchymal transition (EMT), is a very old evolutionary event and the basis for the evolution of complex organisms with many tissues and organs. Organogenesis is not possible without EMT, and thus it is also a central process of trunk development.

* externally funded

Finally, we have started to investigate the effects of genetic variability on disease development. Individual genetic differences have an important impact on whether we are likely to get, for example cancer, where one in three will be affected, or not. We have set out to look for modifiers influencing intestinal tumour formation in the mouse. In addition, we are investigating the evolution and action of modifiers, which trigger male infertility in the mouse and, in combination with a mutant gene, *Tcr*, contribute to non-Mendelian inheritance.

Scientific overview

Regulatory networks controlling trunk development

Trunk formation comprises many processes, such as patterning, endowment of cells with position information, EMT, induction and maintenance of differentiation programs, which are controlled by complex regulatory networks. In principle, three different cell types are involved; stem cells, their descendants, and organizer cells which provide instructive signals. Trunk formation takes place in a growth zone located at the rear (caudal) end of the embryo, called the primitive streak (ps) and, at a later stage, the tail bud (tb). Knowledge about the organization of the ps/tb is still fragmentary. The organizer(s) and stem cells have been localized only roughly, the genetic programs controlling their identities are far from being understood.

In recent years we have put large efforts into developing cell type specific markers, methods and tools for a systematic molecular investigation of tissue differentiation and organ development *in vitro* and *in vivo*. We have performed and completed a large-scale gene expression analysis in E8.5-E11.5 mouse embryos in order to identify the important regulators of differentiation programs and cell specific markers. We have investigated the transcriptome of five regions dissected from E8.5 mouse embryos, providing high-resolution sequence data on all known, and many novel transcription units, including non-coding genes, splice variants, and alternative promoters, to name a few. We have worked out a method for conditional inactivation of gene function based on miRNA-mediated knock-down, allowing the functional analysis of genes involved in embryonic processes. We have introduced and improved the ChIP-seq technique for application on small amounts of tissue typically obtained from embryos, permitting genome-wide analysis of epigenetic modifications. Another advance is the genome-wide localization of chromatin-bound regulators (such as transcription factors and co-factors, chromatin remodelling proteins) by ChIP-seq, enabling the identification of target genes of such regulators. Another important breakthrough in the department was the establishment of a protocol allowing the *in vitro* differentiation of mesodermal cell types, which will be invaluable in analysing and understanding the early events of differentiation from stem cells to a committed cell type. Finally, all these new developments would not deliver interpretable results without the appropriate bioinformatic evaluation tools, which have been developed and setup in our department.

Genetic variability and disease

One important aspect of regulatory networks controlling any process in a multicellular organism is the fact that they differ from individual to individual. This statement becomes quite apparent when we simply consider the differences between human individuals, for instance in size, looks and skills. Individual differences are due to differences in the genome and the regulatory networks expressed



by the genome. Genetic differences not only determine our capabilities, they also have impact on health and disease, e.g. if one develops cardiovascular disease or cancer.

We follow two different approaches to identify modifier genes having an impact on a particular phenotype. One is placed in the field of tumourigenesis, the other in non-Mendelian inheritance.

Modifiers of intestinal tumour formation and progression

In this project we search for modifier genes exerting a global effect on intestinal tumour formation and progression. It is based on the finding that individual genetic differences have a strong impact on susceptibility to disease. It is completely unclear which differences are important, and which are not. It is known that early tumour formation is correlated with changes in the DNA methylation patterns (hypo- or hyper-methylation) of genes, which influences gene expression (up- or down-regulation). Therefore we set out to search for factors affecting gene methylation, gene expression, and tumour number or phenotype. We assume that there is a good chance to find genes controlling all three aspects. The system we are using to introduce genetic variability, influencing tumour formation and gene control, into the genome is the so-called chromosome substitution (consomic) strain system developed by J. Forejt in Prague. It consists of 27 mouse strains in which a single chromosome or chromosomal sub-region of a *Mus musculus* strain (PWD) was introduced into the *Mus domesticus* inbred strain C57BL/6. In essence, all strains differ by only one chromosome or less from the C57BL/6 strain. We use a mouse model of colon cancer, the APC^{Min} mouse, which has a pure C57BL/6 genetic background, to ask if any of the PWD-derived chromosomes carried by the consomic strains expresses a modifier(s) influencing the formation or phenotype of tumours in the APC^{Min} mouse. This, we have found, is indeed the case. Now we can investigate what these factors are and if they also influence epigenetic modifications and gene expression. This project has the potential to reveal a pathway or network controlling susceptibility to tumour formation and progression in the mouse, which may become important for developing anticancer drugs in the future.

Modifiers of non-Mendelian inheritance and male fertility

Details of the system and approaches can be obtained in the research report of the Transmission ratio distortion group. Here I want to point out the principal important aspects of the project in terms of understanding the evolution of modifiers and how they can trigger a disease phenotype. We have isolated four modifiers having a strong impact on the motility of sperm. These modifiers have co-evolved to produce a strong phenotype, almost exclusive transmission of a particular chromosomal region, the so-called t-haplotype. This phenotype depends on the activity of another important gene, the t-complex-responder (Tcr), which can rescue a sperm cell from the negative action of the modifiers. However, in the absence of Tcr the combined action of several (probably six) such modifiers can trigger a disease phenotype, male sterility. Each modifier alone contributes only approximately 10-15% to the phenotype, and sperm cells can tolerate modifier activity to some degree. Too much activity, however, leads to imbalance and triggers the disease.

The four modifier loci we have isolated evolved by different genetic alterations; gene amplification, switch between alternative promoters leading to up- and down-regulation of alternative transcripts, gene inactivation and a point mutation resulting in a dominant negative protein. The modifiers act on two signalling pathways, one activating and one inhibitory, controlling parameters of sperm motility. It is

quite striking how they interact to produce this phenotype. The inhibitory pathway is down-regulated, while the activating pathway is up-regulated by the modifiers, thus reinforcing each other.

It is conceivable that similar mechanisms may be involved in triggering multifactorial disorders in humans. Thus, studying the modifiers of non-Mendelian inheritance and male fertility can teach us a lesson about the molecular basis of multi-factorial disease.

Cooperations within the Institute

Dept. of Vertebrate Genomics

- Jörn Glökler: *SELEX for binding sites of transcription factors required for murine axis development*
- Christina Grimm: *NGFNplus Consortium: Modifiers; Establishment of primary cell lines from consomic mouse strains*
- Christina Grimm, Silke Sperling: *Screen for genes expressed in the heart, and OPT of mutant mouse hearts*
- Heinz Himmelbauer, Florian Mertes, T. Nolden: *Analysis of gene expression in the mouse embryo*
- Zoltán Konthur: *Selection of phage displayed antibodies for specific detection of Smok/ Tcr; Selection of Aptamers/Intrabodies affecting signal transduction pathways (together with S. Krobitsch, Otto Warburg Laboratory)*
- Bodo Lange, together with Ulrike Korf, DKFZ: *NGFNplus Consortium: Mutanom*
- Hans Lehrach: *NGFNplus Consortia: Modifiers; Mutanom. Individualized medicine on cancer patients*
- Markus Ralser: *Generation of mutant ES cell lines by gene targeting*
- Christoph Wierling: *Computer model of the segmentation clock in the mouse*

Dept. of Human Molecular Genetics

- Andreas Kuss, Lars Jensen: *Analysis of gene expression*

Dept. of Comput. Molecular Biology

- Alexander Schliep, Ruben Schilling: *Development of standard 3D models of mouse embryos for automated annotation of morphology and gene expression via 3D registration of volume data (OPT)*

Research Group Development & Disease

- Mateusz Kolanczyk: *OPT of mouse NF1 mutant cartilage and bone, and of Nox mutant fetuses*
- Georg Schwabe, Daniel Birker: *OPT of Dsh (Shh hypomorphic) mutant mouse embryos*
- Sigmar Stricker: *OPF of chick organs over-expressing muscle regulatory genes*

Otto Warburg Laboratory

- Sylvia Krobitsch: *Yeast-two-hybrid screening*
- Ulrich Stelzl: *Yeast-2-Hybrid Screen for factors interacting with regulators of embryonic development or factors involved in non-Mendelian inheritance; Interactions of t-haplotype molecules; Identification of protein-protein-interactions*

Next Generation Sequencing Group

- Bernd Timmermann: *Transcriptome analysis of the t-haplotype.*

Electron Microscopy Group

- Rudi Lurz: *Localization of the Tcr-protein and transcript in testis and sperm; Electron microscopic analysis of mouse tissues*



Transmission ratio distortion

(Established: 11/2003)



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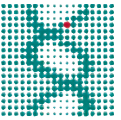
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Scientific overview

Current state of research and scientific findings

A considerable proportion of wild mice carry two variant forms of chromosome 17, the wild type and the *t*-form. Males heterozygous for the *t*-haplotype transmit this chromosome at a high ratio to their offspring, at the expense of the wild type chromosome. This is in opposition to Mendel's laws, according to which two homologous chromosomes are transmitted at equal rates to the offspring. Thus trans-

* externally funded



In addition, we identified a positive regulator of Rho proteins as a transmission ratio distorter in the *Tcd2* region. This gene, *Fgd2* (*faciogenital dysplasia 2*) encodes a GEF (guanosine nucleotide exchange factor). GEFs activate Rho proteins by promoting the exchange of GDP for GTP (Bauer et al., *Genes & Development*, 2007).

The *t*-forms of *Tagap1* and *Fgd2* represent hypermorphic alleles, and both promote the transmission ratio of the *t*-haplotype. Since the two factors have contrary effects on their respective G-protein, but act additively, we conclude that they act on two different G-proteins, which exert opposite effects on Smok1 (Fig 2, Bauer et al., *Genes & Development* 2007).

We have also shown that *Tcd2* similar to *Tcd1* is composed of more than one gene. Analysis of a second candidate gene revealed its activity as a transmission ratio distorter (*Tcd2b*). Unlike *Tagap1* and *Fgd2*, the *t*-form of *Tcd2b* is phenocopied by a knock-out allele suggesting, that the *t*-allele encodes a hypomorph. We are currently analyzing whether this gene acts as a negative regulator of the activating (*Fgd2*-) pathway (Fig 2, Bauer et al., unpublished). Since spermatozoa derived from *t/+* males show impaired flagellar function, we suggest that *Tcd2b*, along with, *Tagap1* (*Tcd1a*), *Tcd1b* and *Fgd2* act in signalling pathways controlling sperm motility. We propose a model, in which the *Distorters* hyperactivate Smok1, compromising sperm function. *Tcr* acts as an “antidote”, bringing the signalling pathway back to a level favourable for normal flagellar function (Fig. 2).

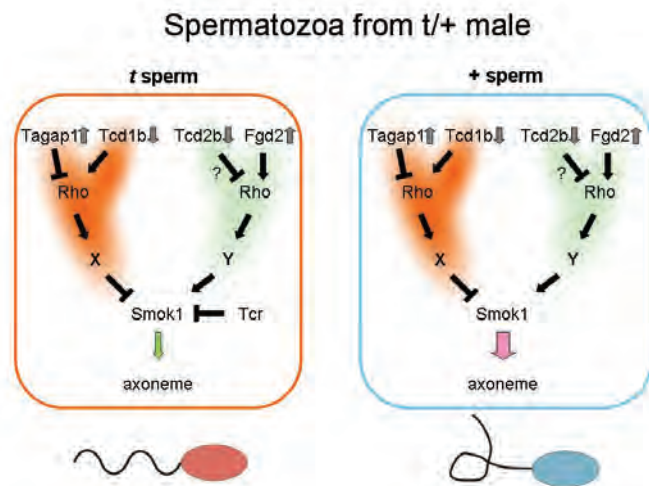


Figure 2: Signaling events in Transmission ratio distortion. Distorters hyper-activate Smok1 via two distinct pathways: They reduce the activity of a Smok1 inhibitory pathway (left branch, red shade), and promote activity of a Smok1 activating pathway (right branch, green shade). Synergistic hyperactivation of Smok1 by the two pathways leads to compromised sperm function in all cells since Distorter molecules are distributed between *t*-spermatogenic cells and their meiotic partners (see Fig 1b). *Tcr*, a dominant negative version of the Smok1 kinase counterbalances hyperactivated Smok1 and thus rescues specifically *t*-sperm (left) to which its gene products are restricted (see figure 1). Hypermorphic and hypomorphic *Tcds* are symbolized with grey upward and downward arrows respectively. Three of the four distorters known to date (*Tcd1b*, *Fgd2*, *Tcd2b*) have been characterized in the period 2006 – 2009.

General information

Selected publications

Verón N., Bauer H., Weisse A., Lüder G., Werber M. & Herrmann B.G. (2009) *Retention of gene products in syncytial spermatids promotes non-Mendelian inheritance as revealed by the t-complex-responder*. Genes & Development 23:2705-2710

Bauer H., Veron N., Willert J. & Herrmann B.G. (2007). *The t-complex-encoded guanine nucleotide exchange factor Fgd2 reveals that two opposing signaling pathways promote transmission ratio distortion in the mouse*. Genes & Development 21, 143-7.

Bauer H., Willert J., Koschorz B. & Herrmann B.G. (2005). *The t-complex-encoded GTPase-activating protein Tagap1 acts as a transmission ratio distorter in mice*. Nature Genetics 37, 969-73.

Work as scientific referee

Herrmann Bauer serves as scientific referee for the journal Development Genes and Evolution.

Patent

Herrmann B.G., Bauer, H. *Isolation of the t-complex distorters and applications thereof*. No: PCT/EP 2006/007977, August 2005.

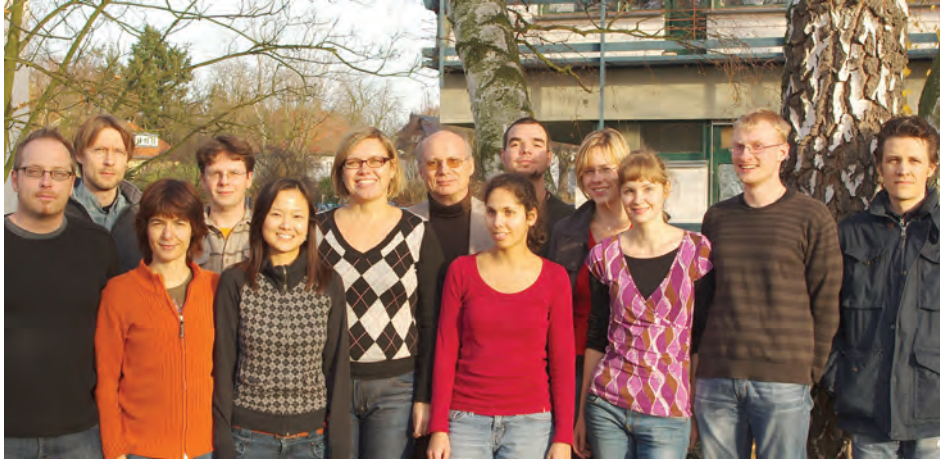
External funding

DFG grant HE 1751/4-2 - 1751/4-4 to Bernhard G. Herrmann (10/09-09/12)



Regulatory Networks of Mesoderm Formation & Somitogenesis

(Established: 11/2003)



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Arnold Schröder (10/03 – 10/09)
Benedikt Schwartz (01/07 – 09/08)

Introduction

The formation of complex organisms from a single cell requires tight control of multiple reiterative steps of cell proliferation, patterning and differentiation, comprising frequent cell interactions and changes of the cellular readout. Trunk development involves a large repertoire of cellular responses controlled by competing signaling pathways, which employ different sets of transcriptional regulators forcing cells into various differentiation pathways. Developmental geneticists in general use mutagenesis tools to remove or alter the function of single genes to be able to analyse their roles in embryogenesis (provided a phenotype is observed). Often the knowledge gained from such analyses ends at the description of the phenotype. However, advances in genomics research have set the stage for gaining deeper insight into the genetic control of developmental processes, even of such complexity as trunk formation. To reach a deeper understanding of the regulatory networks controlling complex cellular interactions and responses leading to tissue and organ development, we have set up a number of techniques allowing the faster generation and analysis of mutants, derive genome-wide datasets of epigenetic gene control and gene expression, and analyse differentiation programs and regulatory networks *in vivo* and *in vitro*.

* externally funded

Scientific overview

We have recently completed a large-scale expression screen in mouse embryos investigating the temporal and spatial control of several thousand genes in day 8.5 – 11.5 mouse embryos. The data are publicly available in the MAMEP database. This herculean task was undertaken to determine the molecular anatomy of the mouse embryo and thereby identify the genes controlling patterning, differentiation and organogenesis. The data are invaluable in deciphering regulatory networks controlling these processes.

The database on individual gene expression patterns was recently complemented by and extended to whole transcriptome data on five tissues (head, heart, somites, spinal cord, presomitic mesoderm) dissected from E8.5 mouse embryos. A genome wide sampling of transcriptional activity was obtained by deep sequencing of RNA on an Illumina GAIIX station (RNA-seq). Bioinformatics analysis enabled annotations of all known and many novel transcription units, including non-coding genes, splice variants, alternative promoters and novel long range spanning RNAs. Moreover, we complemented this transcriptome dataset by genome-wide histone modification landscape data obtained by deep sequencing of immunoprecipitated chromatin (ChIP-seq). We obtained an unmatched catalog of genome activity on the expression and chromatin level in the developing murine embryo. Throughout the analysis and evaluation of RNA-seq and ChIP-seq data we developed many important bioinformatics tools and established computational workflows that are crucial for effective utilisation of these large scale data sets.

In addition to the above, we have also developed a vector system allowing manipulation of cultured cells or embryos by conditional (spatially and temporally controlled) expression of wild-type or mutant genes from transgene constructs integrated as single copy genes into a defined recipient locus. Another technical advance is the development of a vector system for conditional down-regulation of gene transcripts using miRNA-mediated gene knock-down. These methods are complemented by advanced embryological techniques allowing the production of chimera, which are almost exclusively derived from ES cells. This technique permits the immediate functional analysis of the consequences of genetic alterations, introduced into ES cells *in vitro*, in chimaeric embryos derived from such ES cells, thus avoiding time consuming establishment of transgenic mouse lines.

Finally, we have invested in the development of an *in vitro* differentiation system, which allows the mass production of different cell types from embryonic stem cells in the culture dish. This technology is essential for providing sufficient cellular material of early stages of differentiation, which in the mouse embryo occur in very few cells. The combined advances in technology introduced into our approaches now permit us to manipulate embryonic stem cells, differentiate them *in vitro* to particular cell types and study the genetic/epigenetic events controlling the differentiation program, or use the cells to produce embryos and study the differentiation program *in vivo*. We can manipulate the processes by changing gene expression and gene function, and analyse the genetic/epigenetic effects of these alterations *in vitro* and in the embryo. Such analyses will allow us to unravel the regulatory networks controlling stemness, induction, commitment and differentiation into various cell types. Trunk development involves patterning processes leading to the formation of several transient stem cell types: preneural cells, presomitic, lateral and intermediate mesoderm, and endoderm from epiblast stem cells. The patterning process is controlled by two main signaling cascades, WNT and BMP signaling. Within hours the transient stem cell types become committed to differentiation into neural tissue (spinal cord), somites (precursors of skeletal muscle, cartilage and bones of the axial skeleton), somatopleure and splanchnopleure, gonads and kidneys, and

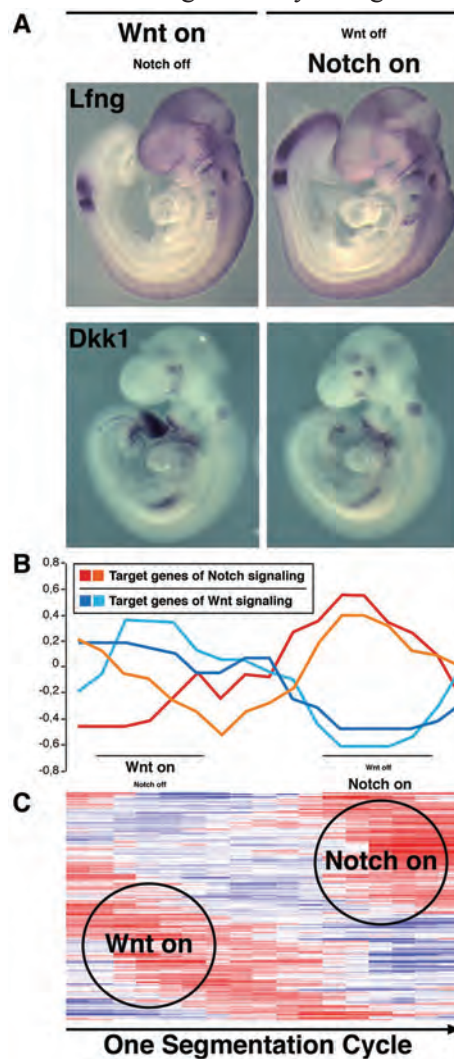


the midgut and hindgut. These early patterning events set the stage for subsequent differentiation processes, in a strictly hierarchical manner. Therefore, understanding the early patterning events during trunk formation will provide essential knowledge about the control of tissue and organ development in general.

Presomitic mesoderm formation and patterning

Our primary focus so far was on understanding the formation and segmentation of presomitic mesoderm (psm). This is a highly integrated process controlled by the WNT signal cascade. We have analysed the hierarchy of several transcriptional regulators, which play an essential role in psm formation, and showed that signal molecule Wnt3a controls this process in cooperation with the downstream transcriptional regulators T, Tbx6 and Msn1. Of course, many more genes are involved in the regulatory networks controlled by these factors. For a detailed analysis of this differentiation process we use a combination of target gene identification and chromatin analyses using ChIP-seq, RNA-seq analyses of wild-type and mutant tissue as well as *in situ* gene expression data.

Somitogenesis divides the presomitic mesoderm into a regular array of segments, cellblocks, which are aligned on either side of the neural tube and undergo pairwise fusion to form vertebrae. Tight spatial and temporal control of psm segmentation is essential for the formation of a well shaped vertebral column. We have shown that the segmentation process is also controlled by WNT signaling, and that psm development and segmentation are highly integrated processes. Wnt3a plays a double role in the segmentation process: it forms a morphogen gradient and drives an oscillator, which together define where the position of the segment boundary, the separation between neighboring cellblocks, is set. The oscillator is defined by the cyclic activity of three interacting signal pathways, WNT, FGF and Notch. Though many components of and interactions between these pathways have been described, there is still debate about the molecular mechanisms controlling the segmentation process. It is not known what is the pacemaker of the oscillator nor what keeps neighboring cells synchronized. We work on these fundamental questions. We have cooperated with Christoph Wierling and Ralf Herwig from the Lehrach department to model the oscillator in the computer, further improving our understanding of the crosstalk between signaling cascades involved in the oscillator.



General information

Selected publications

EW Deutsch, CA Ball, JJ Berman, GS Bova, A Brazma, RE Bumgarner, D Campbell, HC Causton, J Christiansen, F Daian, D Dauga, DR Davidson, G Gimenez, YA Goo, S Grimmond, T Henrich, BG Herrmann, MH Johnson, M Korb, JC Mills, AJ Oudes, HE Parkinson, LE Pascal, N Pollet, J Quackenbush, M Ramialison, M Ringwald, D Salgado, SA Sansone, G Sherlock, CJ Stoeckert, Jr., J Swedlow, RC Taylor, L Walashek, A Warford, DG Wilkinson, Y Zhou, LI Zon, AY Liu, LD True (2008). *Minimum Information Specification For In Situ Hybridization and Immunohistochemistry Experiments (MISFISHIE)*. Nature Biotechnology 26, 305-312

Kolanczyk M, Kossler N, Kuhnisch J, Lavitas L, Stricker S, Wilkening U, Manjubala I, Fratzl P, Spörle R, Herrmann BG, Parada L, Kornak U, Mundlos S. (2007). *Multiple Roles for Neurofibromin in Skeletal Development and Growth*. Hum Mol Genet 16, 874-86

L Wittler, E Shin, P Grote, A Kispert, A Beckers, A Gossler, M Werber & BG Herrmann (2007). *Expression of Msgn1 in the presomitic mesoderm is controlled by synergism of WNT and Tbx6*. EMBO Reports 8, 784-789

JK Dale, P Malapert, J Chal, G Vilhais-Neto, M Maroto, T Johnson, S Jayasinghe, P Trainor, B Herrmann & O Pourquie' (2006). *Oscillations of the Snail Genes in the Presomitic Mesoderm Coordinate Segmental Patterning and Morphogenesis in Vertebrate Somitogenesis*. Developmental Cell 10:355-66

Grote, P & Conradt B (2006). *The PLZF-like protein TRA-4 cooperates with the Gli-like transcription factor TRA-1 to promote female development in C. elegans*. Dev Cell 11, 561-573.

Selected memberships

B.G. Herrmann is elected member of EMBO

Work as scientific referee

B.G. Herrmann serves as referee for the following journals: Biomed Central Developmental Cell, Developmental Dynamics, Development Genes and Evolution, FEBS Journal, Genes & Development, Genetical Research Cambridge, Genome Biology, Mechanisms of Development, MoD Gene Expression Patterns, Nucleic Acids Research.

Membership in journal editorial boards

- Development Genes & Evolution (co-editor until 2009)
- GENES (Open Access Journal)

Service to scientific community

B.G. Herrmann serves as referee for the following Science Organizations and Institutions: Deutsche Forschungsgemeinschaft (DFG), EMBO, Eidgenössische Technische Hochschule Zürich (ETH), GEN-AU (Austrian Genome Research Program), RIKEN, Swiss National Science Foundation, The Wellcome Trust

Spin-offs

B.G. Herrmann is Co-Founder of ALACRIS Pharmaceutical GmbH (founded in Berlin 2008)

External Funding

BMBF, Rare Diseases: *CURE-Net*, 02/2009-01/2012 (Wittler/Herrmann)

BMBF, NGFNplus: *Modifier SP2*, 06/2008 - 05/2011 (Herrmann)



BMBF, NGFN-2: *SMP-RNAi*, 01/2005-07/2008 (Herrmann)

BMBF, NGFN-2: *SMP-DNA*, 11/2004-05/2008 (Herrmann)

BMBF, NGFN-2: *SMP-RNA*, 11/2004-05/2008 (Herrmann)

Organisation of scientific events

Day of science, MPI for Molecular Genetics: Grote, Schwartz

Public relations

Bernhard Herrmann: interviews and expert information for Deutschlandfunk, Süddeutsche Zeitung, Wirtschaftswoche, interviews for TV

Lange Nacht der Wissenschaft (Long Night of Sciences): Introduction to vertebrate embryology, organized by Wittler and Spörle, supported by many members of the department; since 2005

Hosting the artist Gaby Schulze collaborating with the MPIMG (with Dr. Urban), Spörle 2005-2009

Advanced Training for Teachers: MNU Congress 2009, Berlin (talk by H. Bauer)

Hosting School Classes: *A Day in the Lab*; Bauer, Wittler, Schrewe 2007, 2008, 2009

Signal Transduction in Embryogenesis and Tumour Progression

(Established: 05/2005)



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Introduction

In embryonic development, signalling networks interact in a controlled manner to specify cell fates. During tumour formation and progression, oncogenic mutations perturb such signals. As a consequence, the balance between stemness, proliferation, differentiation and apoptosis is lost in the tumour. The mouse is an excellent model to study vertebrate development and disease, due to the availability of inbred and consomic strains, a complete and annotated genome sequence, and the ability to modify the genome by transgenic techniques. In our projects, we expand the toolkit of mouse genetics and genomics and apply innovative methods to study tumour initiation and progression in the mouse.

Scientific Overview

Inducible and tissue-specific transgenesis and RNAi in the mouse

In this project, we have developed an integrated system for mouse transgenesis, consisting of a tetracycline-dependent on/off switch and a cassette for recombinase-mediated cassette exchange (RMCE) in a single genomic locus. We have employed the system for the integration of transgene and RNA interference cassettes, which subsequently can be expressed under the control of doxycycline. We have

* externally funded



generated mice from embryonic stem cells carrying the transgene system and demonstrated inducibility and efficacy of RNA interference *in vivo*, with minimal off-target effects.

Importantly, the modular nature of the single-locus RMCE transgene system will allow a wide array of applications, including general or tissue-specific transgene overexpression and RNA interference in the embryo and in the adult mouse. Mouse models based on this integrated vector system have several advantages over conventional transgenics, such as transgene insertion lines or conditional knock-out mouse lines: the use of tissue-specific promoters and/or an inducible tet-system allows a high degree of control of transgene expression. In addition, transgenic mice can be directly derived from transgenic embryonic stem cells, providing mouse models with a uniform genetic background. Finally, crossing of transgenic mice will generate offspring with a high percentage (50%) of transgenic animals, unlike other complex genetic systems that rely on several transgenes in different genomic locations.

Systematic analysis of oncogenes in the mouse (Mutanom)

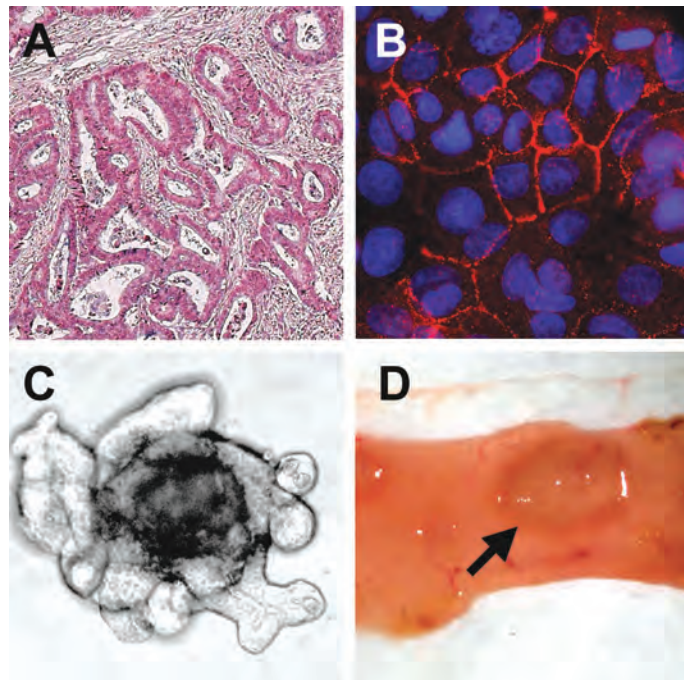
High-throughput sequencing approaches have recently isolated a plethora of mutations in tumour genomes. Functional studies however have mainly focussed on a few of these mutations up to now. The NGFNplus project Mutanom aims at the systematic functional characterisation of somatic mutations in breast, prostate and intestinal cancer cells.

We complement this systematic approach in cancer cell biology by analysing key mutations in tumour-prone mice, using the RMCE transgene system for the expression of mutated oncogenes in the intestine and the mammary gland. The possibility of systematic *in vivo* analysis of the roles of selected oncogenic mutations in the mouse will likely unravel important aspects of tumour biology that cannot be assessed in cell culture or in retrospective analysis of human tumour samples.

Modifiers of intestinal tumour formation and progression

The individual genetic background is known to have a major effect on the lifetime risk of developing cancer, and on cancer progression. The genetics of cancer susceptibility are however complex (polygenic), and thus it is almost impossible to assess the influence of the individual genetic background of humans on the lifetime risk of developing this disease.

We use two powerful new tools for genetic analysis, B6/PWD chromosome substitution strains and ultrahigh-throughput sequencing (Solexa) to isolate genetic traits that affect intestinal cancer initiation and progression in the APC^{Min} mouse, which is an established model for human intestinal cancer. In the first phase of the project, we have



Experimental options for the analysis of intestinal tumour initiation and progression. (A) Retrospective analysis of tumour tissue. A section of human metastatic colon carcinoma is shown; (B) Cell culture. Photo shows immunofluorescence of the cell adhesion molecule E-cadherin in SW480 colon carcinoma cells. (C) Intestinal crypt culture established from untransformed mouse intestine. (D) Mouse tumour models. Arrow points to adenoma in the intestine of a APC^{Min} mouse.

found that PWD genomic sequences protect APC^{Min} mice from intestinal cancer. We have subsequently mapped multiple tumour modifiers to individual mouse chromosomes and sub-chromosomal regions. In co-operation with the Department of Vertebrate Genomics (Lehrach) the intestinal tumour transcriptome and epigenome of mice carrying modifiers is analysed. Our newly developed system for RMCE will facilitate the generation of mouse models with an uniform genetic background for validation of modifier candidate genes. Ultimately, such research will allow to define genetic networks of tumour susceptibility and progression, and thus, to define high- and low-risk groups among colon cancer patients.

A loss of function phenotypic screen for EMT and metastasis genes in intestinal tumour cells

Key signalling pathways, such as Wnt, Fgf and Tgf-beta signalling pathways instruct cells in the embryo to execute specific developmental programs and acquire appropriate phenotypes. One key phenotypic switch during embryonic development is epithelial-to-mesenchymal transition (EMT): cells that undergo EMT lose apical-basal polarity, re-organize their cytoskeleton, down-regulate cell adhesion, and become motile. Tumour progression to metastasis involves EMT-like changes in tumour cell morphology and involves similar signalling pathways and key molecules.

We have utilized a loss of function phenotypic screen to assess the effect of approx. 400 EMT candidate genes from the embryo on SW480 intestinal tumour cells. Our esiRNA-based approach allowed for the first time to screen a large number of EMT candidate genes in a simple functional assay. Multiple genes involved in tumour progression were isolated, highlighting the similarity between EMT in embryogenesis and tumour metastasis. We currently focus on the role of Fgf signals in intestinal cell biology and have delineated signalling cascades and downstream target genes of Fgf in the intestine, using tumour cell lines and primary organ culture. We have found an essential role for Fgf signals for the maintenance of a mesenchymal, motile phenotype in intestinal tumour cells.

Perspectives

Our work focusses on intestinal tumour initiation and progression, combining modern high throughput methods with innovative mouse models. Over the last years, we have established or gained access to a wide array of resources, such as *in vivo* RNAi and tissue-specific transgene systems in the mouse, an exhaustive library of oncogenes, second generation sequencing methods, and intestinal crypt culture. We are therefore well equipped to elucidate signalling networks that control cell homeostasis, proliferation and differentiation in the normal and transformed intestine.



General Information

Selected publications

Fritzmann J., Morkel M., Besser D., Budczies J., Kosel F., Brembeck F.H., Stein U., Fichtner I., Schlag P.M., Birchmeier W.: *A colorectal cancer expression profile that includes transforming growth factor beta inhibitor BAMBI predicts metastatic potential*. Gastroenterology 2009 Jul; 137(1):165-175. (M. Morkel is equally contributing principal author)

Chmielowiec J., Borowiak M., Morkel M., Stradal T., Munz B., Werner S., Wehland J., Birchmeier C., Birchmeier W.: *c-Met is essential for wound healing in the skin*. J Cell Biol 2007 Apr 9; 177(1):151-162.

Pohlars M., Truss M., Frede U., Stehle M., Kuban R.J., Hoffmann B., Morkel M., Birchmeier C., Hagemeyer C.: *A role for E2F6 in the restriction of male germ cell specific gene expression*. Current Biology 2005 Jun 7; 15(11): 1051-1057.

Morkel M., Huelsken J., Wakamiya M., Ding J., van de Wetering M., Clevers H., Taketo M.M., Behringer R.R., Shen M.M., Birchmeier W.: *Beta-catenin regulates Cripto- and Wnt3-dependent gene expression programs in mouse axis and mesoderm formation*. Development 2003 Dec;130(25):6283-6289.

Work as scientific referee

M. Morkel serves as scientific referee for the International Journal of Cancer.

External funding

BMBF, NGFNplus: *Modifier SP 5*, 06/2008 - 05/2011 (Morkel)

BMBF, NGFNplus: *Mutanom*, 06/2008-05/2011 (Morkel/Herrmann)

Fundacao para a Ciencia e Tecnologia (PhD grant to Joana de Campos Alves Vidigal)

Organogenesis

(Established: 09/2004)



Head

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Pedro Veliça (Marie Curie Fellow,
University of Birmingham, UK; 10/
2006 – 4/2007)
Sebastiano Battaglia (Marie Curie
Fellow, University of Birmingham,
UK; 7/2008 – 4/2009)

PhD Students

Michaela Mayer (since 06/2005)
Pedro Rocha* (since 01/2007)

Technician

Manuela Scholze*

Scientific overview

Organogenesis is the process by which complex and highly specialized structures develop from a small population of undifferentiated embryonic cells. The understanding of the role of signaling pathways, specific and general transcriptional regulators, and cellular interactions in cell proliferation, cell differentiation, cell migration, and development of organs is important for understanding tissue regeneration and repair, and ultimately for growing organs in culture.

Functional analysis of Slit-like 2 (Slit2) in organogenesis

The Slit2 protein is a typical single-pass type I transmembrane protein. Its extracellular amino-terminal end contains a putative hydrophobic signal peptide, one leucine-rich repeat (LRR) region comprising ten leucine-rich repeats flanked by an amino- and a carboxy-terminal LRR motif, one epidermal growth factor (EGF) repeat, and a fibronectin type III (FNIII) domain. It shows structural similarities to Slit, a secreted cell guidance molecule, isolated and characterized first in *Drosophila*. It was shown that the human Slit2-homologue Vascularin can bind to TGF- β 1 and negatively modulate TGF- β signaling. We generated a comprehensive temporal and spatial expression pattern by describing not only endogenous *Slit2* expression, but also reporter gene expression in *Slit2-LacZ* knock-in and in *Slit2-Venus*-BAC transgenic mice. These three approaches produced consistent results and

* externally funded



revealed defined expression from early embryonic stages onwards, suggesting an essential role for *Slit12* in the mouse. And indeed, *Slit12*-deficient mice, generated *via* classical gene targeting in ES cells, die within 3-4 weeks after birth. We are currently investigating the molecular basis and identifying the pathways leading to the early postnatal death.

Role of Med12 in mouse development

The Mediator complex is commonly seen as a molecular bridge that confers information from transcription factors bound to regulatory regions of genes to the RNA polymerase II machinery assembled on the promoter of these genes. It is a large complex of 30 subunits, some of which seem to play a structural role in the complex and are therefore generally required for transcription. Other subunits, however, are thought to be responsible for specific interactions with defined transcription factors. Med12 is ubiquitously expressed in the embryo (Fig. 1A, B) and in adult tissues (Fig. 1C). The ability of Med12 to bind β -catenin suggests a role in Wnt signaling. Sox9, Gli3, and Sox32 are other factors that have been shown to bind to Med12, and the activation of their target genes is dependent on this interaction. We have targeted the *Med12* gene on the X chromosome in male mouse embryonic stem (ES) cells and generated two *Med12*-mutant alleles, namely *Med12^{lox-neo}*, a hypomorphic allele, and the conditional *Med12^{lox}*, which behaves as a wild-type allele. Embryos derived from hypomorphic *Med12* mutant ES cells by tetraploid aggregation die around embryonic day 10.5 (E10.5) and have a drastic reduction in Med12 protein levels. We are currently characterizing its function during mouse development and its interaction with other transcription factors like Sox9, and Gli3, that use Med12 as their anchor to the Mediator complex.

Perspectives

We will continue our studies of *Slit12* and *Med12* mutants by expression profiling and marker gene expression analyses. Microarray data derived by comparing wild-type and mutant expression profiles will be verified by whole-mount *in situ* hybridization and immunohistochemical techniques. Tissue-specific mutations will be generated by crossing the conditional mutant mice with various Cre recombinase-expressing mouse lines. Resulting tissue-specific mutant embryos and mice will be characterized using the above mentioned techniques.

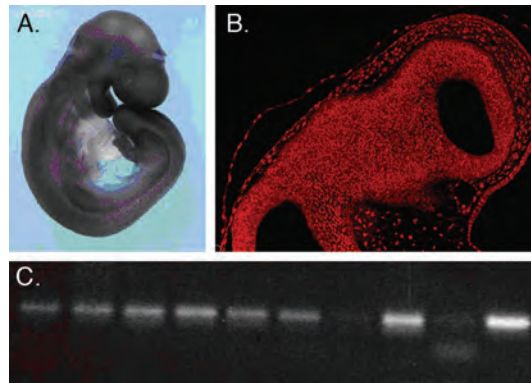


Figure 1: Expression of Med12 in embryonic and adult tissues. (A) Mouse E9.5 embryo with Med12 expression detected by whole-mount *in situ* hybridization (source: MAMEP database). (B) Nuclear Med12 expression in the head region of a E9.5 mouse embryo visualized by fluorescent immunohistochemistry using a α -Med12-specific antibody. (C) RT-PCR shows ubiquitous expression of Med12 in adult mouse tissues (from left: ovary, spleen, small intestine, large intestine, liver, brain, heart, kidney, lung, skin).

General information

Selected publications

Birtwistle, J., Hayden, R.E., Khanim, F.L., Green, R.M., Pearce, C., Davies, N.J., Wake, N., Schrewe, H., Ride, J.P., Chipman, J.K. & Bunce, C.M. (2009). The aldo-keto reductase AKR1C3 contributes to 7,12-dimethylbenz(a)anthracene-3,4-dihydrodiol mediated oxidative DNA damage in myeloid cells: implications for leukemogenesis. *Mutat. Res.* 662, 67-74.

Khanim, F.L., Hayden, R.E., Birtwistle, J., Lodi, A., Tiziani, S., Davies, N.J., Ride, J.P., Viant, M.R., Günther, U., Mountford, J.C., Schrewe, H., Green, R.M., Murray, J.A., Drayson, M.T. & Bunce, C.M. (2009). *Combined bezafibrate and medroxyprogesterone acetate: Potential novel therapy for acute myeloid leukaemia*. PLoS ONE (in press)

Veliça, P., Davies, N.J., Rocha, P.P., Schrewe, H., Ride, J.P., and Bunce, C.M. (2009). *Lack of functional and expression homology between human and mouse aldo-keto reductase 1C enzymes: implications for modelling human cancers*. *Molecular Cancer* (in press)

Janssen, A., Hoellenriegel, J., Fogarasi, M., Schrewe, H., Seeliger, M., Tamm, E., Ohlmann, A., May, C.A., Weber, B. H. & Stöhr, H. (2008). *Abnormal vessel formation in the choroid of mice lacking tissue inhibitor of metalloprotease-3*. *Invest. Ophthalmol. Vis. Sci.* 49, 2812-2822.

Awards

P. Rocha: *Mercy Speer Award for best talk at 6th International Conference on Neural Tube Defects*, 2009

External funding

EC, NucSys, Marie Curie Research Training Network, 01/2006 - 12/2009

Medical Research Council, UK, 10/2004 - 09/2007

Work as scientific referee

H. Schrewe serves as referee for the following journals: *Journal of Cell Sciences*, *PLoS ONE*, and *MoD Gene Expression Patterns*.

Organization of scientific events

6. International NucSys Meeting in Berlin (June 20 - 22, 2008) (organizer: H. Schrewe)



General information about the whole Department

Complete list of publications (2006-2009)

2009

Birtwistle, J., Hayden, R.E., Khanim, F.L., Green, R.M., Pearce, C., Davies, N.J., Wake, N., Schrewe, H., Ride, J.P., Chipman, J.K. & Bunce, C.M. (2009). The aldo-keto reductase AKR1C3 contributes to 7,12-dimethyl-benz(a)anthracene-3,4-dihydrodiol mediated oxidative DNA damage in myeloid cells: implications for leukemogenesis. *Mutat. Res.* 662, 67-74.

Khanim, F.L., Hayden, R.E., Birtwistle, J., Lodi, A., Tiziani, S., Davies, N.J., Ride, J.P., Viant, M.R., Günther, U., Mountford, J.C., Schrewe, H., Green, R.M., Murray, J.A., Drayson, M.T. & Bunce, C.M. (2009). *Combined beza-fibrate and medroxyprogesterone acetate: Potential novel therapy for acute myeloid leukaemia.* PLoS ONE (in press)

Krawczyk J, Goesmann A, Nolte R, Werber M., Weisshaar B (2009). *Trace2PS and FSA2PS: two software toolkits for converting trace and fsa files to PostScript format.* Source Code Biol Med. 2009 Jul 21;4:4. PubMed PMID: 19622158; PubMed Central PMCID: PMC2722627

Nandy C., Mrázek J, Stoiber H, Grässer FA, Hüttenhofer A & Polacek N (2009). *Epstein-barr virus-induced expression of a novel human vault RNA.* J Mol Biol 388 (4); 776-784.

Veliça, P., Davies, N.J., Rocha, P.P., Schrewe, H., Ride, J.P., and Bunce, C.M. (2009). *Lack of functional and expression homology between human and mouse aldo-keto reductase 1C enzymes: implications for modelling human cancers.* Molecular Cancer (in press)

Verón N., Bauer H., Weisse AY., Lüder G., Werber M & Herrmann BG (2009). *Retention of gene products in syncytial spermatids promotes non-Mendelian inheritance as revealed by the t-complex-responder.* Genes Dev 23:2705-2710.

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Charron Y., Madani R, Combepine C, Gajdosik V, Hwu Y, Margaritondo G & Vassalli J-D (2008). *The serpin Spn5 is essential for wing expansion in Drosophila melanogaster.* Int J Dev Biol 52(7):933-42.

EW Deutsch, CA Ball, JJ Berman, GS Bova, A Brazma, RE Bumgarner, D Campbell, HC Causton, J Christiansen, F Daian, D Dauga, DR Davidson, G Gimenez, YA Goo, S Grimmond, T Henrich, BG Herrmann. MH Johnson, M Korb, JC Mills, AJ Oudes, HE Parkinson, LE Pascal, N Pollet, J Quackenbush, M Ramialison, M Ringwald, D Salgado, SA Sansone, G Sherlock, CJ Stoeckert, Jr., J Swedlow, RC Taylor, L Walashek, A Warford, DG Wilkinson, Y Zhou, LI Zon, AY Liu, LD True (2008). *Minimum Information Specification For In Situ Hybridization and Immunohistochemistry Experiments (MISFISHIE).* Nature Biotechnology 26, 305-312

Janssen, A., Hoellenriegel, J., Fogarasi, M., Schrewe, H., Seeliger, M., Tamm, E., Ohlmann, A., May, C.A., Weber, B. H. & Stöhr, H. (2008). *Abnormal vessel formation in the choroid of mice lacking tissue inhibitor of metalloprotease-3.* Invest. Ophthalmol. Vis. Sci. 49, 2812-2822.

Wittler L*, Saborowski M & Kessel M (2008). Expression of the chick Sizzled gene in progenitors of the cardiac outflow tract. *Gene Expr Patterns* 8(6), 471-476.

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H Bauer. N Véron. J Willert. BG Herrmann (2007). *The t complex-encoded guanine nucleotide exchange factor Fgd2 reveals that two opposing signaling pathways promote transmission ratio distortion in the mouse.* Genes Dev 21, 143-147

Gurok U, Bork K, Nuber U, Spörle R, Nöhring S & Horstkorte R (2007). *Expression of Ndufb11 encoding the neuronal protein 15.6 during neurite outgrowth and development*. Gene Expression Patterns 7, 370-374.

Kolanczyk M, Kossler N, Kuhnisch J, Lavitas L, Stricker S, Wilkening U, Manjubala I, Fratzl P, Spörle R, Herrmann BG, Parada L, Kornak U, Mundlos S. (2007). *Multiple Roles for Neurofibromin in Skeletal Development and Growth*. Hum Mol Genet 16, 874-86

L Wittler, E Shin, P Grote, A Kispert, A Beckers, A Gossler, M Werber & BG Herrmann (2007). *Expression of Msn1 in the presomitic mesoderm is controlled by synergism of WNT and Tbx6*. EMBO Reports 8, 784-789

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Charron Y, Madani R, Nef S, Combepine C, Govin J, Khochbin S & Vassalli J-D (2006). *Expression of Serpinb6 serpins in germ and somatic cells of mouse gonads*. Mol Reprod Dev 73(1): 9-19.

JK Dale, P Malapert, J Chal, G Vilhais-Neto, M Maroto, T Johnson, S Jayasinghe, P Trainor, BG Herrmann & O Pourquie' (2006). *Oscillations of the Snail Genes in the Presomitic Mesoderm Coordinate Segmental Patterning and Morphogenesis in Vertebrate Somitogenesis*. Developmental Cell 10, 355-366

Grote, P & Conradt B (2006). *The PLZF-like protein TRA-4 cooperates with the Gli-like transcription factor TRA-1 to promote female development in C. elegans*. Dev Cell 11, 561-573.

Simonin Y, Charron Y, Sonderegger P, Vassalli J-D & Kato AC (2006). *An inhibitor of a serine proteases, neuroserpin, acts as a neuroprotective agent in a mouse model of a neurodegenerative disease*. J Neurosci 26(41): 10614-19

PhD theses

2009

Michaela Mayer: *Functional analysis on the role of Slit-like 2 (Slit2) in the mouse*. PhD Thesis, Freie Universität Berlin, 10/2009 (supervisor: Heiner Schrewe)

2008

Solveig Müller: *Funktionelle Charakterisierung regulatorischer Gene bei der Bildung der Wirbelsäule der Maus*. PhD Thesis, Freie Universität Berlin, 09/2008 (supervisor: Bernhard Herrmann)

Nathalie Véron: *Untersuchungen zu den molekularen Grundlagen der nicht-mendelschen Vererbung in der Maus*. PhD Thesis, Freie Universität Berlin, 12/2008 (supervisor: Bernhard Herrmann and Hermann Bauer)

Student theses

2009

Oliver Sedelmeier: *Systematic analysis of Mettl-gene expression during mouse embryo development*. BSc Thesis, Beuth Hochschule für Technik, Berlin, 09/2009 (supervisor: Philipp Grote)

Judith Proske: *Molekulare Analyse von Genen, die eine mögliche Funktion in der Ausbildung von urorektalen Fehlbildungen während der Säugerembryogenese haben*. Diploma Thesis, Univ. Osnabrück, 2009 (supervisor: Lars Wittler)

2008

Sabrina Schindler: *Etablierung von micro RNA-Konstrukten zur Genexpressionskontrolle von Smok1, Tagap1 und Fgd2*. Diploma Thesis, Technische Fachhochschule Berlin, 2008 (supervisor: Hermann Bauer)

Susanna Sluka: *Analysis of intestinal tumor initiation and progression in APCmin/chromosome substitution strain C3, C12 and C17 mice*. Master Thesis, Humboldt University / Charité - Universitätsmedizin Berlin, 11/2008 (supervisor: Markus Morkel)



2007

Christof Bernemann: *Beta-Catenin/APC kontrolliert die Expression von Kandidatengenenen für epithelial-mesenchymale Transition in der intestinalen Karzinogenese*. Diploma Thesis, Freie Universität Berlin, 04/2007 (supervisor: Markus Morkel)

Ruben Schilling: *Elastic registration of 3D volume data*, Diploma Thesis, OPT-3D-registration, University of Freiburg, 2007 (supervisor: Alexander Schliep, Dept. of Computational Molecular Biology, together with Ralf Spörle)

2006

Michael Plötz: *Analyse zur Charakterisierung des Latrophilin-2 Knock-outs*. Diploma Thesis, Freie Universität Berlin, 2006 (supervisor: Heiner Schrewe)

Eun-Ha Shin: *Funktionelle Analyse der Genregulation während der Somitogenese des Wirbeltierembryos*. Diploma Thesis, Institut für Biotechnologie, Technical University Berlin, 09/2006 (supervisor: Bernhard Herrmann)

Teaching activities

Teaching activities at the Charité-Universitätsmedizin Berlin

Preclinical Course: Biology for medical students (each semester term since 2004); Organizer: Schrewe; Tutors: Spörle, Wittler, Bauer, Morkel, Müller, Mayer, Schindler, Shin, Nandy, Proske

Master's Programme: Molecular Medicine (module 3, Developmental Genetics; yearly 3 weeks course since 2006); Organizer: Wittler; Tutors: Bauer, Morkel, Spörle, Neidhardt

Weekend Workshop: Human Genetics (Humangenetik), Charité (since 2006). Tutors: Spörle, Wittler, Grote, Schrewe

Teaching activities at other universities

Wittler: Design of the Module *Developmental Biology of the Vertebrates* as part of the Masters Programme in Molecular Life Sciences, Humboldt University of Berlin; including lecture *Organization of the body axes in the vertebrate embryo*, seminar *animal models in developmental biology* and course *molecular embryology*, summer term 2009

Schrewe: Practical Course: *Developmental Genetics* at the School of Biosciences, University of Birmingham, UK (annually since 2004)

Schrewe: Practical Course: *Embryonic Stem Cell Culture* at the Max-Planck Institute for Molecular Genetics, Berlin (6/2007 and 6/2008)

Teaching activities at the MPIMG

PhD Programme, Course 3: *Developmental Genetics* (1 week) Tutors: Morkel, Bauer, Schrewe, Grote, Wittler

Literature Tutorial for Students of the Dept. Develop. Genetics (bi-weekly since 1/2009) Tutors: Grote, Wittler, Morkel

