



Research Group Development & Disease

(Established: 05/2000)



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Dr. rer. nat. Uwe Kornak* (since 03/04)
Dr. med. Pablo Villavicencio-Lorini* (since 02/05)
Dr. med. Claus Eric Ott* (since 03/05)
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Dr. rer. nat. Boris Thurisch* (since 08/07)
Dr. rer. nat. Johannes Egerer* (since 09/07)
Dr. med. Peter Krawitz* (since 01/09)
Dr. rer. nat. Pia Kuss* (since 07/09)
Dr. med. Katrin Hoffmann* (01/04-12/09)
Dr. rer. nat. Petra Seemann* (01/06-02/09)
Dr. med. Alexander Jamsheer (06/08-12/08)
Dr. med. Katarina Lehmann* (08/00-03/08)
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Dr. med. Katrin Süring* (07/02-12/04)
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Saniye Yumlu (since 01/09)
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Anja Brehm (10/05-12/09)
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Ulrich Wilkening (06/04-09/09)
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Nicole Verhey van Wijk (01/01-06/06)

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Monika Osswald (since 05/05)
Carola Dietrich (since 10/09)
Maria Walther (02/07-12/09)
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PD Dr. Denise Horn*

Cytogenetics

Dr. med. Seval Türkmen*
Dr. rer. nat. Marc Trimborn*

Molecular Genetics

Dr. rer. nat. Hartmut Peters*

Structure of the group

The research group Developmental & Disease focuses on the mechanisms by which genes control normal and abnormal development. The group is part of and works in close collaboration with the Institute for Medical Genetics (IMG), which is located at the Campus Virchow of the Charité - Universitätsmedizin Berlin. The IMG provides clinical and diagnostic genetic service locally, i.e. for the Berlin-Brandenburg area, as well as internationally. It consists of a unit for Clinical Genetics, Cytogenetics, and Molecular Genetics. Medical doctors in training rotate to work within the Development & Disease group and scientists from the MPIMG have the opportunity to specialize in Medical Genetics at the IMG. A shared infrastructure, exchange of technical achievements and expertise, as well as common research goals ensure a successful interdisciplinary approach to study the mechanisms of genetic disease. Thus, the research group Development & Disease and the IMG form a highly complementary unit that combines clinical expertise with a basic science approach to address genetic questions.

Development and regeneration are related and it is generally believed that developmental pathways get re-activated during healing processes. To synergistically use our expertise in the molecular control of cell differentiation and development with new advances in regenerative medicine we collaborate closely with the Berlin-Brandenburg Center for Regenerative Medicine (BCRT) which is funded by the BMBF. Two members of the lab, Jochen Hecht and Petra Seemann, were appointed as group leaders at the BCRT but remain affiliated with the group.

Research concept

The mechanisms by which DNA sequences influence human development, function and aging has moved into the center of medical research creating the basis for what is now called molecular medicine. Much of what we have learned over the past years is based on the knowledge about the human as well as other genomes and the use of model systems. However, understanding the pathomechanisms of human disease is frequently challenging due to complexity of the systems and limited transferability. We aim at combining basic biology, genetics and clinical medicine to generate in-depth knowledge of human diseases, especially those related to abnormal development (congenital malformations) and growth and homeostasis of the skeleton.

The research group at the MPI develops and analyzes genetically engineered *in vitro* and *in vivo* models to elucidate pathogenetic mechanisms for human disease. Through the IMG clinical and diagnostic services patient cohorts are generated that are analyzed for genetic defects. This involves patient recruitment, expert phenotyping, data management and analysis, as well as mutation detection, mapping, and disease gene identification. The latter has profited greatly from the recent technology developments at the MPIMG such as array-CGH and next generation sequencing. The identification of an ever increasing number of rare, potentially disease causing mutations necessitates in-depth functional analysis of the identified changes. At the Development & Disease group we are well equipped to test novel disease genes/mutations for their functional relevance in established *in vitro* and *in vivo* model systems. The major *in vivo* systems are genetically engineered mice, chicken embryos and, more recently, zebrafish. Thus, our approach synergistically combines basic science oriented research at the MPI with the more clinically oriented work at the IMG for research into human genetic disorders.



Scientific achievements / findings

Our research focuses on normal and abnormal mechanisms that influence development, growth, homeostasis, aging, and regeneration of the skeleton. The skeleton is a particularly informative model system for our phenotype driven approach, because of an almost unlimited number of distinct phenotypes. Over the past years our aim has been to learn about the origins of phenotypic variability, develop new definitions for disease entities in order to better predict the phenotype from the genotype. To achieve these goals the department is set up as an interactive unit with close cooperation between all members of the different research groups. Currently, our focus is on the following topics:

Molecular pathogenesis of the brachydactyly disease family

Brachydactyly (BD) refers to a limb malformation characterized by shortening of digits. We have been studying this group of conditions extensively over the last years to understand their molecular pathology (Fig. 1). Based on human phenotypes and families we identified a number of causes for various types of BDs. Our studies show that most of these conditions are due to mutations in genes of the bone morphogenetic protein (BMP) pathway, or in genes that interact with this pathway. These include mutations in the bone morphogenetic protein receptor *BMPR1B*, its ligand *GDF5*, a regulatory element in *BMP2*, the BMP antagonist *NOGGIN*, the transcription factors *HOXD13* and *SOX9*, as well as the tyrosine kinase receptor *ROR2*. We have established mouse and *in vitro* models for most of these genes and investigated the developmental pathology of mutations and the normal gene action during mouse and chicken development. Our studies have shown that variability within this group of conditions is due to a general dysregulation of the pathway. Depending on whether the BMP signal is increased or decreased and on the ratio of receptor signaling different phenotypes arise. In addition, we identified basic mechanisms that control digit outgrowth such as the phalanx forming region which was shown to be controlled by Smad signaling. Based on these studies we have proposed the concept of molecular disease families defined as conditions that share certain phenotypes due to a common pathway dysregulation.

Sigmar Stricker has been studying the role of *Ror2* in this process as well as basic mechanisms of digit development. Petra Seemann concentrated on the role of BMPs in digit and joint development.

Hox genes in limb development

Homeobox genes, and the proteins they encode, the homeodomain proteins, play important roles in the developmental processes of many multicellular organisms. Some of these genes have been shown to play important roles in limb development. However, it has remained a continuous challenge in the field to establish where Hox genes fit into the molecular genetic program of patterning and organogenesis of the limb elements.

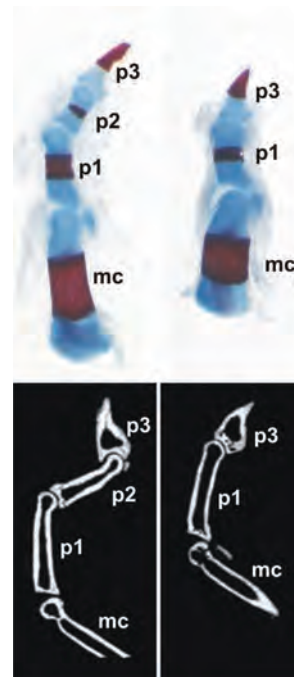


Figure 1: The *Ror2*-brachy mouse, a model for human brachydactyly. Skeletal preparations are shown on top, individual digits are labeled P1, P2, P3. Metacarpal is mc. μ CT scan of digits (bottom panel). Note missing middle phalanx (P2) in mutant (right).

In humans, mutations in HOXD13 results in synpolydactyly, a limb malformation characterized by an additional finger between digits 3 and 4 and a fusion of these three digits. The mutations that cause this condition are rather unusual as they comprise expansions of a polyalanine tract in the N-terminal region of the HOXD13 protein. We have studied the nature of this mutation in a mouse mutant that carries the exact same mutation found in humans (spdh) as well as in other Hox mutant mice. We showed that Hoxd13 regulates Raldh2, an enzyme critical for retinoid acid (RA) synthesis in the limb and that, consequently, RA is reduced in mutant limbs. RA is produced in the interdigital space where it suppresses chondrogenesis. The relevance of this finding was supported by the fact that treatment of pregnant mice with RA resulted in restoration of pentadactyly in spd mice.

In a second set of experiments we showed that Hox genes control bone formation in the limbs by directly activating Runx2, the transcription factor essential for bone formation. Furthermore, we demonstrate that Hox genes determine the shape and identify limb bones and that their inactivation causes a homeotic transformation of long bones (metacarpals) into round bones (carpals). Together, our findings show that Hox genes are essential modifiers of shape and limb gestalt by controlling stem cell differentiation into chondrocytes or osteoblasts.

Pia Kuss and Pablo Villavicencio-Lorini have been the driving force in this project.

Mechanisms of bone regeneration

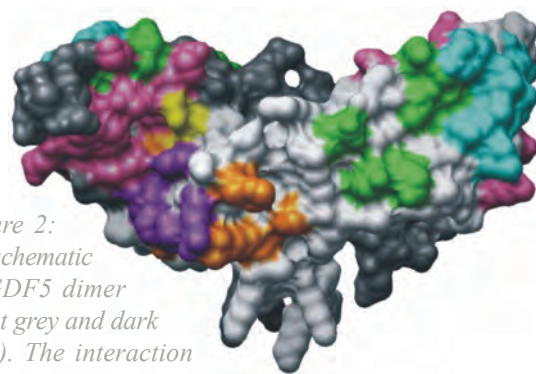


Figure 2:
3D-schematic
of GDF5 dimer
(light grey and dark
grey). The interaction
face with the BMP-receptors
type I (orange/red) type II (green) and Noggin (pink) are
color-coded. Alteration of amino acid N445 (yellow) dis-
rupts the NOG interaction site and result in a GDF5 mol-
ecule that is no longer inhibited by NOG.

Bone has the unique capability to regenerate after injury. Considerable evidence indicates that the molecular control of this process uses similar pathways as during bone development. It is our aim to investigate these processes in order to understand regeneration and to develop new tools to improve bone healing in patients. We have been investigating gene regulation during fracture healing in the sheep using high throughput sequencing and have analyzed the data using bioinformatic tools. These data have given first insights into the genetic control of fracture healing. BMPs have been used for some time to

improve bone formation. However, in some individuals their effect is limited and large amounts of the protein are needed. Based on our findings with the GDF5 mutations we have been developing new BMPs with improved biological activity, for example by manipulating the receptor specificity of by creating BMPs that are resistant to inhibition by e.g. Noggin (Fig. 2). These new BMPs are currently being tested in animal models.

Jochen Hecht and Peter Robinson have been working on the fracture model, Petra Seemann on the improvement of BMPs.

Osteoporosis and mechanisms of aging

In humans aging is invariably accompanied by changes in skin and bone. While age-related skin wrinkling is rather a cosmetic problem, age-related bone loss results in a increased susceptibility to fractures and thus a significant disease burden. To elucidate the molecular processes that govern aging in these tissues, we studied a group of recessively inherited diseases collectively characterized by the combination of wrinkly skin and osteoporotic bone. Over the last years we have



been able to identify disease causing mutations in three different genes, two of which are involved in the Golgi network. Mutations in the $\alpha 2$ subunit of the vacuolar-type proton pump (H(+)-ATPase or V-ATPase) ATP6V0A2 were shown to be associated with wrinkly skin syndrome. This pump is present in Golgi secretory vesicles and appears to be important for the proper protein modification, as patients with mutations in the gene show abnormal serum protein glycosylation pattern. In a similar condition, geroderma osteodysplastica, we identified mutations in GORAB, a novel Rab6 interacting golgin. Through further mapping analysis we identified a third group of patients with overlapping wrinkly skin phenotypes and identified mutations in PYCR1, the gene coding for the enzyme that catalyzes the NAD(P)H-dependent conversion of pyrroline-5-carboxylate to proline (pyrroline-5-carboxylate reductase). Further investigation *in vitro* and *in vivo* (zebrafish, xenopus) showed that the enzyme is located exclusively in mitochondria and that inactivation resulted in increased rates of cell death (Fig. 3). Intriguingly, similar observations were made in ATP6V0A2 mutant cells which show intracellular accumulation of secretory cargo and increased cell death.

Our findings provide new insights into the molecular mechanisms of skin aging and osteoporosis. Proper function of the Golgi apparatus appears to be important for maintenance of healthy skin. Increased susceptibility to apoptosis may be an important trigger for age-related changes in skin and bone.

Uwe Kornak is in charge of this project.

Long range regulation

Most developmentally important genes have complex expression patterns that show distinct differences in temporal and spatial distribution. How this is achieved is largely unknown but cis-regulatory enhancer and suppressor elements are believed to play an important role. By screening large cohorts of patients with limb malformations *via* array-CGH we have identified a series of duplications involving conserved non-coding elements (CNEs) that are located in the vicinity of developmentally important genes. Sonic hedgehog (Shh) is a morphogen expressed asymmetrically in the posterior limb bud margin where it contributes to the overall bauplan of the autopod by determining the number and identity of digits. Shh is surrounded by a large gene desert containing numerous conserved elements that presumably act as enhancers. We identified duplications in one of these regions that are associated with duplicated and triphalangeal thumbs. In a large family with brachydactyly type A2 we identified a small (5 kb) duplication 3' of the BMP2 gene. A highly conserved sequence within this duplication was shown to drive expression in the distal digits suggesting that a dosage effect is causative for the phenotype (Fig. 4). Furthermore, in a limb malformation syndrome with absent nails and missing middle phalanges (Cooks syndrome) we identified a 1Mb duplication 5' of the SOX9 gene, a gene previously associated with a lethal skeletal dysplasia with sex reversal.

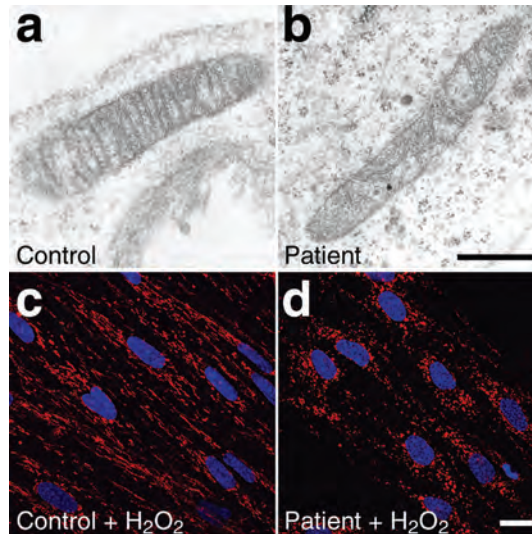


Figure 3: Electron microscopy of mitochondria from skin fibroblasts from a control (a) and a patient (b) with a mutation in PYCR1. Note abnormal structure of mitochondria. Challenge of the cells with reactive oxygen species (H_2O_2) results in disintegration of mitochondria (red staining) in the patient's fibroblasts (d), but not in control cells (c).

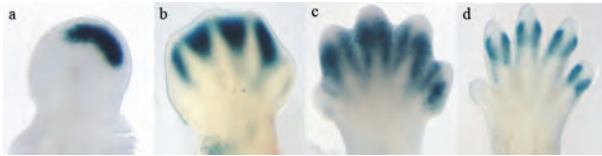


Figure 4: X-Gal staining of transgenic mice carrying the brachydactyly associated duplicated region of BMP2 at various stages of limb development. Staining is first visible in the progress zone of the limb bud (a), then between the digit anlagen (b), and finally around the phalanges with highest staining around the middle phalanges (c, d).

Our findings identified duplications of CNEs as a novel mutation mechanism for human disease. In addition, they show that CNEs are important for fine tuning expression and that alterations in these regions can result in unexpected phenotypes. Alterations of regulatory CNEs are a likely mechanism for evolutionary change.

Eva Klopocki is in charge of this project.

Medical bioinformatics

Our group has developed an ontology to describe the phenotypic features seen in hereditary and other forms of human disease. This manually curated program can be used to study phenotypic features with bioinformatic tools and other forms of computational analysis. Following its publication in November 2008, the Human Phenotype Ontology (HPO) was featured as a research highlight in Nature Reviews Genetics and is already being adopted by international research groups for phenotyping, including most prominently the DECIPHER group at the European Bioinformatics Institute/Sanger Center. We have more recently used the HPO to develop a clinical diagnostics algorithm for human genetics that utilizes a novel statistical model of semantic similarities in ontologies to provide a ranking of the candidate differential diagnoses and have developed a novel graph algorithm that accelerates semantic searches in ontologies by many orders of magnitude. A patent application for a number of applications of these algorithms was recently submitted to the United States patent office. In addition, our bioinformatics group is active in a number of other areas including algorithms and support for ChIP-seq and other next generation sequencing applications as well as analysis of microRNA and mRNA microarray hybridizations and promoter analysis.

Peter Robinson leads the bioinformatics group.

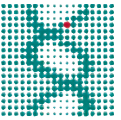
Identification of disease genes

Our aim is to identify genetic factors that cause or modify monogenic diseases. Learning about the cause of a disease helps to understand, or to start to study, the subsequent disease processes and aims to develop more effective diagnostics and eventually preventive or therapeutic strategies. We have been using traditional linkage analyses, candidate gene sequencing, and array-CGH, and have now applied sequence capture and subsequent massive parallel sequencing to identify disease causing genes. With a sufficient supply of patient material this provides us with a continuous flow of novel genes and mutations. This project is interdisciplinary and involves clinicians for sampling, diagnosing, and phenotyping as well as bioinformatics for the analysis of phenotypic and sequence data, and sequencing technology for mutation identification.

Denise Horn represents the clinical aspect of this project, Nick Robinson and Katrin Hoffmann the bioinformatic part, and Jochen Hecht is in charge of the sequencing. Peter Krawitz has established analysis routines for improving detection of indels in Illumina/Solexa data and for using the exon-enriched NGS sequencing for clinical diagnostics.

Cooperation within the institute

Cooperations over the past years have been with the Lehrach Dept. on a EU-funded large scale gene expression study using automated *in situ* hybridization technology (Maire-Laure Yaspo), the Evolution and Development group (Georgia



Panopoulou, Albert J. Poustka) on the evolution of Runx genes, and with Michal Schweiger (Cancer Genomics) on disease gene identification. We have been cooperating with the Herrman Dept. on novel technologies for 3D bone imaging. There is a long standing cooperation with the Ropers Dept. on array-CGH and the genetic causes of mental retardation. Close cooperations exist with the Vingron Dept. on computational analysis of ChIP-Seq data, analysis of sequencing data, ontologies and the role of a novel mitochondria localized gene. Together with Knud Nierhaus we are investigating the role of a novel ribosome-associated protein. Intense collaborations exist with the mouse and the sequencing facilities.

Special facilities / equipment

The research group as well as the IMG is equipped with the standard facilities for research into genetics, developmental biology, cell biology, and molecular biology. Special equipment includes the histology unit for the MPIMG and a sequencing facility for the Charité.

Planned developments

Future developments will aim at the integration of biological and phenotypic data. To achieve an in depth understanding of disease mechanisms we will aim at saturating disease groups by systematically analyzing phenotypes and disease genes/mutations. With an increasing number of conditions/genes we will be able to better understand the complexities of the dysregulated pathway(s) and their resulting phenotypes. To achieve this goal we will combine novel phenotyping methodology such as the HPO and screen patient samples using high throughput mutation analysis such as array-CGH, sequence capture, and whole exome/genome sequencing. Using this approach we will be able to combine phenotypic and molecular data in a systematic and comprehensive manner allowing us to better understand and ultimately predict the consequences of mutations.

General information about the whole group

Complete list of publications (2006-2009)

2009

Seemann P., Brehm A., Kulas J., Reissner C., Stricker S., Kuss P., Renninger S., Groppe JC, Plöger F, Pohl J, Schmidt von Kegler M., Walther M., Gassner I, Rusu C, Janecke AR, Dathe K & Mundlos S. *Mutations in GDF5 Reveal a key Residue Mediating BMP Inhibition by NOGGIN.* PLOS Genetics 2009 Nov; 5(11): e1000747

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Awards

Stefan Mundlos:

- Maroteaux Award, International Skeletal Dysplasia Society (2009)

Anja Brehm:

- 1. International BMP workshop 2009 Luzie Fabisch Award (2009)

Eva Klopocki:

- Young Scientist's Award, European Society of Human Genetics (2009)
- Vortragspreis 2009, Deutsche Gesellschaft für Humangenetik (2009)
- Finalistin Trainee Award, American Society of Human Genetics (2009)

Uwe Kornak:

- Ian T. Boyle Award of the European Calcified Tissue Society (ECTS) (2007)

Petra Seemann:

- Otto Hahn Medaille (2007) of the Max Planck Society

Work as scientific referee

S. Mundlos work as scientific referee for the following journals: Nature Genetics, American Journal of Human Genetics, American Journal of Medical Genetics, European Journal of Genetics, Journal of Medical Genetics, Human Genetics, Clinical Genetics, Development, Developmental Dynamics,

Mechanisms of Development, Journal of Clinical Investigation, Human Molecular Genetics, Histochemistry, Bone, Experimental Cell Research.

Membership in journal editorial boards

- American Journal of Medical Genetics
- Clinical Genetics
- Histochemistry

Service to scientific community

S. Mundlos serves as a referee for the following science organizations and institutions: Deutsche Forschungsgemeinschaft (DFG), Bundesministerium für Bildung und Forschung (BMBF), Wellcome Trust, European Union, Boltzmann Institute, Swiss National Science Foundation.

Postdoctoral lecture qualification (Habilitation) 2009

Katrin Hoffmann (2009) *Kopplungsanalysen zur Aufklärung monogener und komplexer Krankheiten*

Peter N. Robinson (2009) *Molekulare und klinische Untersuchungen beim Marfan Syndrom und verwandten Erkrankungen*

2008

Georg Schwabe (2009) *Molekulare Grundlagen von Organmalformationen am Beispiel kongenitaler Extremitätenfehlbildungen und eines Lateralisierungsdefekts*

2007

Denise Horn (2009) *Syndromale Erkrankungensbilder mit mentaler Retardierung*

PhD theses 2009

Florian Witte (2009) *Analyse der Ror2-Funktion in vivo und in vitro - Die Ror2 W749X-Maus als Modell für humane Brachydaktylii Typ B*. PhD Thesis

Uli Wilkening (2009) *Funktionelle Analyse von in der Skelettentwicklung differentiell regulierten Genen*. PhD Thesis

Chayarop Supanchart (2009) *Characterization of an Osteopetrosis mouse model*. PhD Thesis

Friederike Kremer (2009) *Nonsense-mediated mRNA decay in collagen X*. PhD Thesis

Pia Kuss (2009) *Molekulare Pathologie und Embryologie von Hoxd13-assoziierten Fehlbildungen der Extremitäten*. PhD Thesis

Charlotte Wilhelmina Ockeloen (2009) *Split hand/split foot malformation: determining the frequency of genomic aberrations with molecular-genetic methods*. PhD Thesis

2008

Seval Türkmen (2008) *Molekulare Analyse genetisch bedingter Entwicklungsstörungen*. PhD Thesis

Haikuo Zhang (2008) *Investigating the molecular mechanism underlying Geroderma osteodysplastica (GO) Syndrome*. PhD Thesis

2007

Andreas Ney (2007) *Zur Pathogenese des Marfan Syndroms: Untersuchung der Matrix-Metalloproteinase-Regulierung nach Stimulierung mit rekombinanten Fibrillin-1-Konstrukten und Untersuchung der Selbstassoziation eines rekombinanten Versikan-Konstruktes*. PhD Thesis

2006

Petra Seemann (2006) *Zur Bedeutung des Wachstumsfaktors GDF5*. PhD Thesis

Nicole Verhey van Wijk (2006) *Identifizierung intrazellulärer Bindungspartner von Ror2*. PhD Thesis

Jochen Hecht (2006) *Genexpressionsanalysen zum besseren Verständnis von Knochenheilung und -entwicklung*. PhD Thesis



Student theses

2009

Julia Meier (2009) *Die Etablierung eines siRNA-Systems zur funktionellen Analyse der Odd-skipped-related-Gene Osr1 und Osr2 am Beispiel des Hühnerembryos*. Diploma Thesis

Annika Mahl (2009) *Charakterisierung der Interaktion der Rezeptortyrosinkinase Ror2 mit dem Liganden Noggin*. Diploma Thesis

Nadine Gladow (2009) *Molekulargenetische Untersuchungen des NSD1-Promotors bei Patienten mit Sotos Syndrom*. Diploma Thesis

Dajana Lichtenstein (2009) *Deletionsanalyse im NSD1- und FOXL2-Gen bei Patienten mit Sotos- und BPES Syndrom*. Bachelor Thesis

2008

Denise Pankalla (2008) *Histologische und Expressionsanalyse der Mausmutante ank/ank*. Diploma Thesis

Jolike Van Oosterwijk (2008) *Investigation and Characterization of Genomic Aberrations in Patients with Limb Malformations, with Focus on Brachydactylies*. Master Thesis

K. Guse (2008) *Untersuchung des Neurofibromatose Typ1 – Gen Promoters*. Diploma Thesis

Ines Dabow (2008) *Untersuchungen zur Rolle des Transkriptionsfaktors Mef2c in der Skelettentwicklung*. Diploma Thesis

Mareike Trams (2008) *Regulation des Sonic hedgehog durch cisregulatorische Ion range enhancer*. Diploma Thesis

Janine Dokas (2008) *Analyse des Wnt-Signalweges in der Knorpelentwicklung der Mausextremitäten*. Diploma Thesis

2007

B. Mehmedi (2007) *Erzeugung und funktionelle Untersuchungen von Phosphorylierungsstellen im ANK-Protein*. Diploma Thesis

Cindy Ast (2007) *Funktionelle Analysen zur molekularen Pathogenese der*

Fibrodysplasia ossificans progressiva (FOP). Diploma Thesis

Franziska Neuendorf (2007) *Interaktionen von Ror2 mit dem Wnt – Signalweg. 1. Expressionsanalyse der Wnt-Proteine und Antagonisten im Verlauf der frühen Handentwicklung. 2. Interaktionsstudien mit Hilfe von Coimmunopräzipitationen*. Diploma Thesis

Fabian Grammes (2007) *Charakterisierung der PKA Regulation im NF1 Signalweg*. Diploma Thesis

Sören Zeidler (2007) *Charakterisierung von atNOA1*. Diploma Thesis

Anne Baude (2007) *Untersuchungen zur in vitro-Strukturbildung der Pro-Form des humanen Wachstumsfaktors GDF5: Vergleich des Wildtyps mit einer krankheitsassoziierten Variante*. Diploma Thesis

N. Beck (2007) *Kandidatengenanalyse zum Perrault Syndrom*. Diploma Thesis

S. Köhler (2007) *Support Vector Machines for Disease Gene Prediction from Protein-Protein-Interaction Data*, Master Thesis

2006

Manuela Magarin (2006) *Das Down Syndrom – Symptomatik, Expressionsanalyse der Chromosom 21 Gene und funktionelle Charakterisierung knorpelrelevanter Kandidaten*. Diploma Thesis

Julia Haupt (2006) *Analysis of expression and function of the transcription factor odd-skipped related (Osr2) during limb development*. Diploma Thesis

External funding

DFG: SFB 665, Projekt C04: *Klinisch-genetische Untersuchungseinheit*, 07/09-06/13

DFG: *HOXD assoziierte Fehlbildungen*, 07/09-06/12

EU: *Fighting Aneurismal Disease (FAD)*, 06/08-05/12

BMBF: *Netzwerk Neurofibromatosis: TP4: Analyse von PD98059 als potenzielles Therapeutikum*, 02/09-01/12

DFG: *Computational phenotypic analysis*, 10/08-09/11

Fritz Thyssen Stiftung: *ATPase subunit a2*, 07/09-06/11

DFG: *Array CGH-Analyse bei Extremitätenfehlbildungen*, 04/08-04/11

BMBF: *Pathogenese der autosomal dominanten Osteopetrose*, 04/08-03/11

DFG: SFB 760, TP A1: *The molecular biology of fracture healing*, 01/07-12/10

DFG: SFB 760, TP A2: *Improving bone regeneration by modification of BMP-inhibition*, 01/07-12/10

EU: *Berlin Bedrest Study BBR2-2*, 09/07-11/10

BMBF: BCRT (Berlin Center für Regenerative Therapien): TP A: *Basis Research*, 10/06-09/10

DFG: *Cohenlike-Syndrom*, 06/09-05/10

BMBF/Koop. Biopharm: *BiochancePlus: GDF5 für therapeutische Anwendungen*, 10/06-9/09

Children's Tumor Foundation/USA – Young Investigator Award Application: *Role of FGF signaling in the genesis of multiple bone phenotypes in NF1Prx1 mouse*, 07/07-06/09

BMBF: *Skelnet*, 10/06-12/11

EU: *EuroGrow: Pathophysiology of chondrodysplasia resulting from Prx1-Cre mediated knockout of NF1 (Neurofibromatosis 1) gene*, 04/07-03/10

DFG: SFB 577 TP A4: *Craniometaphyseal dysplasia (CMD) - Clinical Variability and Pathogenic Pathways*, 07/01-06/09

DFG: SFB 577 TP A6: *Molecular Pathology and Embryology of HOXD-related Limb Malformations*, 07/01-06/09

DFG: SFB 577 TP A8: *Analysis of the receptor tyrosine kinase ROR2: a central regulator in the brachdactyly disease family*, 07/04-06/09

DFG: SFB 577 TP Z 05: *Central Facility for Animal Model Generation*, 07/04-06/09

DFG, SFB 665: *Projekt A5: Sonic hedgehog regulation during development and in disorders of the nervous system*, 07/05-06/09