

Department of Pediatrics and Adolescent Medicine

Chair of Pediatrics

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Research focus

- Medication safety
- Perinatal programming and early determination of renal and cardiovascular disorders
- Rare endocrine disorders with a focus on growth abnormalities
- Genetic skin diseases of the neonate
- Genomic aberrations in childhood malignancies
- Differentiation pathways during skeletal development
- Experimental and translational imaging
- Perinatal hypoxic brain injury and neuroprotection

Structure of the Chair

Professorships: 5

Personnel: 430

- Doctors (of Medicine): 81
- Scientists: 15 (thereof funded externally: 10)
- Graduate students: 6

Clinical focus areas

- Medical care of preterm and term newborn infants
- Pediatric endocrinology/diabetology
- Pediatric gastroenterology
- Pediatric nephrology
- Neuropediatrics
- Pediatric endocrinology
- Pediatric oncology and hematology

Research

Research at the Department of Pediatrics and Adolescent Medicine is focused on the area of perinatal medicine. This involves disease-oriented experimental, preclinical, and clinical studies. Further main research interests lie in the fields of pediatric endocrinology, oncology, neuropediatrics and pharmacotherapy. The Department has its own clinical trial center which also serves as an accredited institution for professional training in the field of drug information.

Medication safety

PI: Prof. Dr. A. Neubert

We have a long history of research in the area of

pediatric pharmacotherapy, focusing on medication safety (AMTS). Our contribution to the "AMTS-Aktionsplan 2013-2015" (item 16: Development of recommendations for the use of drugs in children particularly in the inpatient care) led to current BMG-funded activities of our Department to establish an evidence-based dosing information database for children in Germany. We are also in charge of the country-wide project "KiDSafe" funded by the Innovation Fonds. Within this project the aforementioned dosing database (pediatric formulary) and other measures to increase medication safety are being evaluated in detail. Moreover, we actively participate in several EU-funded projects (e. g. GAPP, EPTRI, c4c) and have coordinated a multicenter phase 3 study to investigate the use of clonidine as sedative agent in pediatric intensive care units (CloSed; compare own report). The aim of most projects is a pediatric-use marketing authorization for the studied drugs.

Perinatal programming and early determination of renal and cardio-vascular disorders

PI: Prof. Dr. A. Hartner, PD Dr. F. Fahlbusch
Our research aims at elucidating the consequences of an early impairment of organ development for the pathogenesis of diseases during adolescence and adult life. To this purpose, the sequelae of a congenital reduction of nephron numbers or disruption of renal development for the kidney and the cardiovascular system are being studied. We have been focusing on the pathogenetic mechanisms of inflammatory renal disease, hypertension, and heart failure. In further studies, we are attempting to clarify which placental alterations may lead to defects in organ systems of the offspring and can expedite the onset of later disease. These studies are being performed in collaboration with the Perinatal Center of Middle Franconia and the Comprehensive Cancer Center Erlangen-EMN.

Genetic skin diseases of the neonate

PI: Prof. Dr. H. Schneider

Our primary research goal is to identify pathogenetic mechanisms underlying genodermatoses (hereditary disorders of the skin and its appendages) at the molecular level and to develop appropriate therapeutic approaches. Some of these diseases may be associated with life-threatening complications already in the first weeks after birth. In addition to the skin, other organs, such as eye, ear, and lung, are frequently affected by pathogenetic processes. First systematic natural history studies in patients of different age groups allowed the characterization of genotype-phenotype relationships as a prerequisite for specific therapeutic attempts. In DFG-funded projects, we have been investigating the feasibility of prenatal protein replacement or gene therapy in mouse models of epidermolysis bullosa, lamellar ichthyosis, and hypohidrotic ectodermal dysplasia. We coordinated the first

clinical trial in children with hypohidrotic ectodermal dysplasia, a multicenter study to evaluate the safety and efficacy of a recombinant ectodysplasin A1 administered at the earliest stage of postnatal development. Based on promising preclinical data, the results of this clinical trial, and the success of named-patient use case studies, we are currently preparing a phase 3 trial to investigate such protein replacement therapy *in utero*.

Physiology und Pathophysiology of growth disorders

PI: Prof. Dr. J. Woelfle

Growth is a central phenomenon of childhood, which frequently serves as an indicator of health and disease. Conditions affecting physiological growth conditions can result both in reduced growth velocity, with a subsequent risk of developing short stature, but can also result in excessive growth with an increased risk of gigantism and/or tall stature. Within this area we are interested in genetic and epigenetic mechanisms of growth disorders, in particular in alterations of growth hormone receptor signaling and the transcriptional regulation of members of the growth hormone-IGF-1-axis.

Genomic aberrations in childhood malignancies

PI: Prof. Dr. M. Metzler

Cancer cells show characteristic genetic alterations which are important not only for tumorigenesis and disease progression, but also as molecular markers allowing the detection of specific tumor cells – for diagnostic purposes, monitoring of tumor response to therapy, and for relapse recognition. Besides investigating such molecular markers, we have been analyzing germ-line mutations of selected tumor types that predispose to malignancies early in life. As national study center for chronic myeloid leukemia in childhood and adolescence, we are continuing intense research on clinical and biological aspects of this model disease.

Differentiation pathways during skeletal development

PI: Prof. Dr. M. Rauh, Prof. Dr. H. Schneider

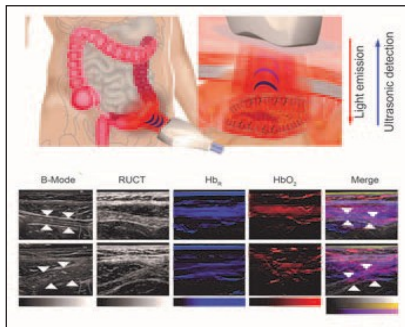
To clarify the role of certain signaling molecules during skeletal development, we have been using a broad spectrum of methods including gene expression assays, immunohistochemistry, models of osteogenesis *in vitro* and *in vivo*, and determination of various enzyme activities by mass spectrometry. A related research project is focused on the controlled differentiation of cord blood-derived mesenchymal stem cells into osteoblasts and chondrocytes. These cells could be used for autografts, e.g. in the treatment of cleft lip and palate (the most frequent congenital malformation) to reduce the number of surgical interventions required.

Experimental and translational imaging

PI: Dr. F. Knieling

Conventional diagnostic imaging methods are often invasive, time-consuming, and harbor risks for complications. These limitations

potentiate in children and adolescents, whose organisms are particularly vulnerable. Light- and sound-based imaging approaches, like multi-spectral optoacoustic tomography (MSOT), offer novel opportunities to perform non-invasive diagnostics. Pulsed laser light in the near-infrared spectrum leads to the generation of ultrasonic waves, which are received by special transducers. Our current projects combine MSOT and other imaging technologies with aspects of basic research and clinical pediatrics to achieve rapid translation of the findings into routine diagnostic procedures.



The principle of multispectral optoacoustic tomography

Neonatal neurology and neuroprotection

PI: Prof. Dr. R. Trollmann

The research of this group is focused on the early detection of perinatally acquired brain lesions and neuroprotection. In an established mouse model of perinatal hypoxia, we have been investigating molecular effector mechanisms of the immature brain after perinatal damage due to hypoxia and excitotoxicity as well as neuroprotective strategies, e.g. administration of erythropoietin and prolyl hydroxylase inhibitors. We are studying the impact of acute hypoxia on early neuronal migration, angiogenesis, astrocytic, and blood-brain barrier function and have been evaluating approaches to pharmacological stabilization of hypoxia-inducible transcription factors (HIF). Moreover, age-specific effects of excitotoxic stimuli on the regulation of excitatory neurotransmitter systems during early development are being characterized in a mouse model of neonatal seizures. The investigation of hypoxia-induced neuroinflammatory mechanisms *in vitro* and in animal models also stimulates the progress of projects on neuroprotective strategies beyond the neonatal period.

Teaching

The Department of Pediatrics and Adolescent Medicine participates with compulsory and elective courses in the degree programs in Medicine and Dentistry. Alongside traditional teaching, special research seminars and interdisciplinary courses are offered. An „emergency care simulator“, adapted to the needs of neonatology and pediatric intensive care, enables the training of emergency medical procedures and team-work analysis of the management strategies applied. This includes regular reviews of real emergency situations experienced in our clinic.

Individual researchers supervise Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Zahn J, Hoerning A, Trollmann R, Rascher W, Neubert A. Manipulation of Medicinal Products

for Oral Administration to Paediatric Patients at a German University Hospital: An Observational Study. *Pharmaceutics*. 2020 Jun 23;12(6):583.

Eberl S, Ahne G, Toni I, Standing J, Neubert A. Safety of clonidine used for long-term sedation in paediatric intensive care: A systematic review. *Br J Clin Pharmacol*. 2020 Dec 23. doi: 10.1111/bcp.14552.

Schmidt M, Rauh M, Schmid M, Huebner H, Ruebner M, Wachtveitl R, Cordasic N, Rascher W, Menendez-Castro C, Hartner A, Fahlbusch FB. Influence of Low Protein Diet-Induced Fetal Growth Restriction on the Neuroplacental Corticosterone Axis in the Rat. *Front Endocrinol (Lausanne)*. (2019) 10:124

Regensburger AP, Fonteyne LM, Jüngert J, Wagner AL, Gerhalter T, Nagel AM, Heiss R, Flenkenthaler F, Qurashi M, Neurath MF, Klymiuk N, Kemter E, Fröhlich T, Uder M, Woelfle J, Rascher W, Trollmann R, Wolf E, Waldner MJ, Knieling F. Detection of collagens by multispectral optoacoustic tomography as an imaging biomarker for Duchenne muscular dystrophy *Nat Med*. 2019 Dec;25(12):1905-1915.

Krieg P, Dick A, Latzko S, Rosenberger S, Meyer J, Crumrine D, Hielscher T, Elias PM, Rauh M, Schneider H. Conditional Alox12b knockout: degradation of the corneocyte lipid envelope in a mouse model of autosomal recessive congenital ichthyoses. *J Invest Dermatol* 2020, 140:249-253 378:1604-1610

Plamper M, Gohlke B, Schreiner F, Woelfle J. Phenotype-Driven Diagnostic of PTEN Hamartoma Tumor Syndrome: Macrocephaly, But Neither Height nor Weight Development, Is the Important Trait in Children. *Cancers (Basel)*. 2019, 11(7):975.

Schulte S, Gohlke B, Schreiner F, Gruenewald M, Fimmers R, Stoffel-Wagner B, Bartmann P, Woelfle J. Thyroid Function in Monozygotic Twins with Intra-twin Birth Weight Differences: A Prospective Longitudinal Cohort Study. *J Pediatr*. 2019 Aug;211:164-171

Jung S, Ballheimer YE, Brackmann F, Zoglauer D, Geppert CI, Hartmann A, Trollmann R. Seizure-induced neuronal apoptosis is related to dysregulation of the RNA-edited GluR2 subunit in the developing mouse brain. *Brain Res*. 2020 May 15;1735:146760. doi: 10.1016/j.brainres.2020.146760.

Jung S, Topf HG, Boie G, Trollmann R. C1 Esterase Inhibitor Reduces BBB Leakage and Apoptosis in the Hypoxic Developing Mouse Brain. *Neuromolecular Med*. 2020 Mar;22(1):31-44. doi: 10.1007/s12017-019-08560-8.

International cooperations

Prof. Dr. T. Grange, Department of Pediatrics, Washington University School of Medicine, St. Louis: USA

Dr. P. Schneider, Department of Biochemistry, University of Lausanne, Epalinges: Switzerland
Dr. O. Delattre, INSERM U830, Institut Curie, Paris: France

Prof. Dr. D. Reinhardt, Department of Anatomy & Cell Biology, McGill University, Montreal: Canada

Prof. Dr. Catherine Tuleu, University College London, London: UK

Prof. Dr. Dick Tibboel, Erasmus Medical Center, Rotterdam: The Netherlands