Department of Pediatrics and Adolescent Medicine

Chair of Pediatrics

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Director
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Research focus
- Medication safety
- Perinatal programming and early determination of renal and cardiovascular disorders
- 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): 75
- Scientists: 15 (thereof funded externally: 10)
- Graduate students: 6

Clinical focus areas
- Medical care of preterm and term newborn infants
- 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 oncology and neuropediatrics. 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, Prof. Dr. W. Rascher
Newborns and infants are particularly at risk for adverse drug reactions and medication errors due to common off-label use and lack of age-appropriate formulations. We have been working for many years on methods to improve medication safety. Data on adverse drug reactions are being collected systematically; high-risk medications have been detected and particularly vulnerable groups of patients have been identified. 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 cardiovascular 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*.

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

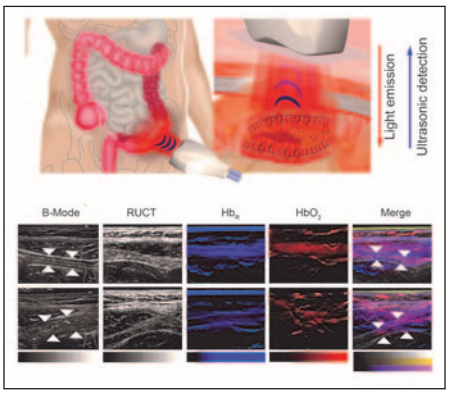
PI: Prof. Dr. M. Rauh, Prof. Dr. H. Schneider
To clarify the role of certain signaling molecules during skeletal development, we have been using a broad spectrum of methods including gene expression assays, immunohistochemistry, models of osteogenesis *in vitro* and *in vivo*, and determination of various 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 multispectral 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

Neubert A, Baarslag MA, Dijk MV, Rosmalen JV, Standing JF, Sheng Y, Rascher W, Roberts D, Winslade J, Rawcliffe L, Hanning SM, Metsvaht T, Giannuzzi V, Larsson P, Pokorná P, Simonetti A, Tibboel D; CLOSED Consortium. The CLOSED trial; CLOnidine compared with midazolam for SEDation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial. BMJ Open 2017, 7:e016031

Hübner H, Strick R, Wachter DL, Kehl S, Strissel PL, Schneider-Stock R, Hartner A, Rascher W, Horn LC, Beckmann MW, Rübner M, Fahlbusch FB. Hypermethylation and loss of Retinoic Acid Receptor Responder 1 expression in human choriocarcinoma. J Exp Clin Cancer Res 2017, 36:165

Knieling F et al. Multispectral optoacoustic tomography for assessment of Crohn's disease activity. N Engl J Med 2017, 376:1292-1294

Schneider H, Faschingbauer F, Schuepbach-Mallepell S, Körber I, Wohlfart S, Dick A, Wahlbuhl M, Kowalczyk-Quintas C, Vigolo M, Kirby N, Tannert C, Rompel O, Rascher W, Beckmann MW, Schneider P. Prenatal correction of X-linked hypohidrotic ectodermal dysplasia. N Engl J Med 2018, 378:1604-1610

Anderson ND et al. Rearrangement bursts generate canonical gene fusions in bone and soft tissue tumors. Science 2018 Aug 31;361(6405)

Trollmann R, Mühlberger T, Richter M, Boie G, Feigenspan A, Brackmann F, Jung S. Differential regulation of angiogenesis in the developing mouse brain in response to exogenous activation of the hypoxia-inducible transcription factor system. Brain Res 2018, 1688:91-102

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