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## Mission and Structure

The Children's Hospital of the University of Würzburg (staff: 67 MD's, 152 nurses, 47 technicians / administrative staff) comprises of 115 beds including a pediatric-neonatal intensive care unit and a neonatal intensive care unit in the perinatal centre (obstetrics and gynecology). The Children's Hospital is divided into the following functional sections: neonatology, pediatric intensive care, oncology / hematology / stem cell therapy, cardiology, pulmonology / cystic fibrosis / sports medicine, gastroenterology, nephrology, endocrinology, diabetes, neuro-pediatrics / social pediatrics, immunology /

infectiology, rheumatology, and others. Every year approximately 6500 patients in the inpatient and 15000 patients in the outpatient setting are being treated. There are many close collaborations to the other institutions of the university hospital.

## Major Research Interests

### Neonatology: Characterization of airway remodeling in acute and chronic lung disease of premature infants and newborns

Surfactant replacement has become a milestone in the treatment of neonatal respiratory distress syndrome (RDS) and has significantly decreased acute pulmonary morbidity and mortality of preterm infants worldwide. Besides improving lung function, surfactant acts as a key modulator of pulmonary innate and acquired immunity thereby regulating lung inflammatory processes. In different studies the effect of new synthetic surfactant preparations on RDS and their immunomodulatory role is characterized. In addition, the role of caffeine on the surfactant system and on airway remodelling processes is analysed (1). Furthermore, translational research involving various animal models has been helpful to answer basic questions concerning the effect of chorioamnionitis on maturation and development of the foetal lung and immune system.

### Pediatric Oncology, Hematology and Stem Cell Transplantation: Cellular immunity and immunomodulation in patients with malignant diseases

The immune system is capable of destroying residual tumor cells after chemotherapy or stem cell transplantation. We analyzed the T-cell function in patients with leukemia or brain tumors and were able to correlate the findings with disease outcome.

Moreover requirements for efficient T-cell priming are analyzed in a robust, antigen-specific in vitro model and the influence of immune response modifiers is studied. As demonstrated for the clinically widely used src-kinase inhibitor dasatinib, interaction of drugs with different players in the immune system can lead to completely disparate effects (Ref. 2, Fig. 1).

We strive to develop new immunotherapies for patients with malignant diseases (dendritic cell vaccination, antigen-specific T-cells), and – in collaboration with the Comprehensive Cancer Center Mainfranken – aim to implement these techniques in clinical studies. A clinical study on tumor-lysate loaded autologous dendritic cells is set to recruit glioblastoma patients in 2014. Within the area of hematopoietic stem cell transplantation, several multicenter studies are performed, focusing on engraftment after haploidentical stem cell transplantation using new methods for graft manipulation. These studies are part of our translational approach to get novel treatment strategies into the clinic (3).

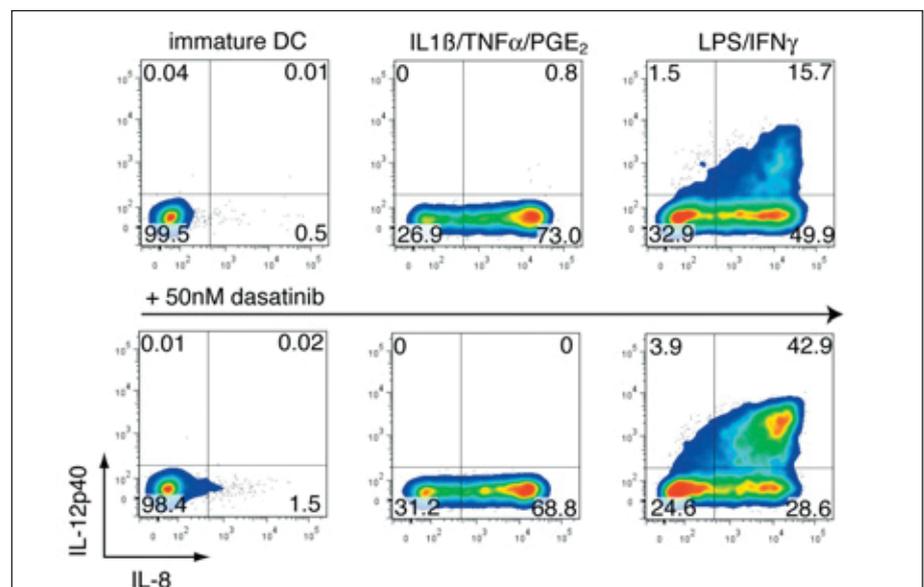


Fig. 1: Intracellular cytokine production in dendritic cells (DC). Stimulation of DC with LPS and interferon- $\gamma$  combined with the src-kinase inhibitor dasatinib synergistically leads to IL-12 production (right). No such synergy is observed with cytokine-matured DC (middle) (Ref.2).

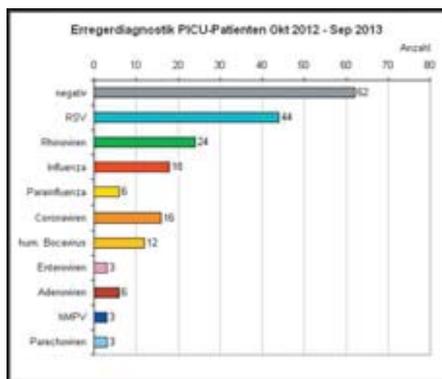


Fig. 2: Frequency of viral pathogens causing acute respiratory infection in 184 patients from paediatric intensive care units (PICU) in Bavaria, identified by multiplex PCR (PICU study, October 12 - September 13). Numbers indicate individual cases.

### Pediatric Infectious Diseases: Epidemiology and prevention of infectious diseases

The burden of pediatric infectious diseases and the effects of vaccination programs on their epidemiology in children and adolescents are evaluated in several prospective studies (main research projects 2012/2013: varicella, pneumococcal disease, influenza, RSV and other viral respiratory infections (see figure 2)). Laboratory samples and clinical data on patient characteristics and severity of disease are collected from a network of hospital and practice pediatricians. Viral and bacterial pathogens types and subtypes are identified, using different molecular-biological methods in collaboration with the Institutes of Virology (Würzburg, Jena) and Hygiene and Microbiology (Würzburg), as well as the National Reference Center for streptococci (Aachen). Adaptations of pathogens, e.g. serotype replacement of pneumococci in pleural empyema under current vaccination programs are investigated.

### Osteology:

#### Hypophosphatasia – pathophysiology and new treatment options

Hypophosphatasia is a rare disease of the bone characterized by reduced phosphatase activity. Bone mineralisation, renal function and possibly CNS function are impaired. Our interdisciplinary team (Children's Hospital/Orthopedic Center for musculoskeletal Research) provides patient care for the largest patient cohort throughout Europe. Research projects range from pathophysiology to preclinical treatment approaches (gene transfer). An international phase II

study for enzyme replacement was initiated in 2011.

### Pediatric Rheumatology: Pathogenesis of rheumatoid and chronic-inflammatory diseases

An imbalance between inflammatory T cells and regulatory T cells is characteristic for T-cell mediated autoimmune disorders. The activation of inflammatory T cells can be modulated by in vitro polarization using various cytokines, by epigenetic modifications and interaction with mesenchymal stem cells. Using these approaches novel therapeutic targets may be identified for the treatment of Juvenile Idiopathic Arthritis and other autoimmune disorders.

Another project is aimed to investigate the role of immunosuppressive/immunomodulatory therapy on effector mechanisms against latent virus infections and on the humoral and cellular immune response to vaccine antigens to improve vaccination schedules for immunocompromised patients.

### Pediatric Pulmonology / Cystic Fibrosis / Sports Medicine:

#### Physical activity and conditioning in healthy children and those with chronic lung diseases

Mesenchymal stem cells might be involved in pulmonary tissue repair processes and could thus mediate positive effects of exercise in chronic lung diseases. Therefore, two research projects addressed the question whether acute exercise can trigger a release of mesenchymal stem cells into the blood stream, comparing patients with cystic fibrosis or asthma to healthy controls. One additional study assessed the physical activity behavior in people with cystic fibrosis and healthy individuals. Two projects evaluated new concepts to improve patient care in cystic fibrosis. In one of these studies, the quality of expert answers to lay questions was determined in a European web-based system (ECORN-CF) (5). In another, still ongoing nationwide project, the effects of introducing case managers plus additional psychological support and exercise counseling into standard therapy are evaluated.

## Teaching

The Children's Hospital of the University of Würzburg offers several courses for medical students. Students have repeatedly evalu-

ated the main lecture in pediatrics as one of the best courses in the faculty of medicine. Prof. Dr. C. P. Speer is authorized to fully train MDs in pediatrics, as well as in neonatology and pediatric intensive care. The heads of the sections for pediatric hematology and oncology, neuropaediatrics, and pediatric pulmonology are qualified to train MDs in their respective subspecialties. The Children's Hospital regularly organizes clinical rounds and educational seminars for pediatricians on a regional and national level. In addition, every year scientific meetings and symposia are organized in Würzburg, e.g. every 3rd year the international symposium "Recent Advances in Neonatal Medicine" with participants from more than 50 nations. Outside of the United States of America this symposium represents the largest scientific forum for neonatology.

## SELECTED PUBLICATIONS

Fehrholz M, Bersani I, Kramer BW, Speer CP, Kunzmann S. (2012) Synergistic effect of caffeine and glucocorticoids on expression of surfactant protein B (SP-B) mRNA. *PLoS One* 7:e51575.

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