Institute of Pathology
Division of Nephropathology

Address
Krankenhausstraße 8-10
91054 Erlangen
Phone: +49 9131 8522291
Fax: +49 9131 8522601
www.nephropathologie.uk-erlangen.de

Head of Division
Prof. Dr. med. Kerstin Amann

Contact
PD Dr. rer. nat. Christoph Daniel
Phone: +49 9131 8522602
Fax: +49 9131 8522600
christoph.daniel@uk-erlangen.de

Research Focus
• Afferent renal innervation
• Cell cycle control in podocytes as a therapeutic target in renal disease
• Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
• The role of DPP4 in renal diseases and cardiovascular damage
• The role of PAR-2 in cardiovascular injury
• Mechanisms of cardiac injury and regeneration
• Role of the receptor GPR126 in heart development
• Cardiac tissue engineering
• Terminal differentiation of heart muscle cells

Structure of the Division
Professorships: 2
Personnel: 30
• Doctors (of Medicine): 6
• Scientists: 9 (thereof funded externally: 6)
• Graduate students: 17

Clinical focus areas
• Diagnosis on kidney biopsies
• Diagnosis on peritoneal biopsies
• Diagnosis on iliac crest
• Lightmicroscopy, immunohistology, electron microscopy

Research
Clinical and experimental cooperations are well established with clinical partners and research groups of UK Erlangen and FAU as well as external cooperators, working in the field of nephrology. Main focus of the Division of Nephropathology is to test molecular hypotheses on experimental and human kidney biopsy material.

Afferent renal innervation
PI: Prof. Dr. K. Amann
In cooperation with Prof. Dr. K. Veelken (Department of Medicine 4) we investigate the role of afferent renal nerves and its control of the sympathetic nerve system. Here we look for the effects of afferent renal innervation on pathobiological changes in the heart using animal models for chronic kidney disease and hypertension. The plasticity of afferent renal innervation will be analyzed by its potential to regenerate. Furthermore, the relevance of afferent renal nerve tracts for heart pathophysiology and cardiac afferent innervation for pathophysiologic renal changes will be analyzed to get a comprehensive understanding of neurogenic aspects of the cardio renal syndrome.

Funding: DFG

Cell cycle control in podocytes as therapeutic target in kidney diseases
PI: PD Dr. C. Daniel, Prof. Dr. K. Amann
Podocytes are highly specialized glomerular cells which are essential for blood filtration. These cells are terminally differentiated, that means they cannot regenerate or replace damaged podocytes by proliferation. In nearly all kidney diseases a progressive podocyte loss is observed. In addition, injured podocytes re-enter into the cell cycle despite its terminal differentiation, but are unable to divide and die. In this project, we try to inhibit cell cycle progression in podocytes to prevent loss of these cells and progression of kidney disease.

Funding: Emerging Fields Initiative (EFI): CYDER

Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
PI: Prof. Dr. K. Amann
This project is performed in collaboration with Prof. Dr. K.F. Hilgers (Department of Medicine 4). Mortality rate is still very high in patients with chronic kidney disease (CKD); it is in fact comparable to that of many cancer patients. Death from cardiac causes is the leading cause of death in these patients. CKD patients show characteristic cardiovascular structural alterations, like left ventricular hypertrophy with reduced myocardial capillary density, increased intercapillary distance, and reduced myocardial ischemia tolerance. Our own data as well as data from the literature indicate that impaired angiogenesis in particular in response to hypertrophy or ischemia plays an important pathophysiological role. Using a well-established animal model of CKD (subtotally nephrectomised rat, SNX), we will investigate mechanisms of CKD-induced impaired angiogenesis.

Funding: DFG

The role of DPP4 in renal diseases and cardiovascular damage
PI: PD Dr. C. Daniel
In cooperation with Prof. Dr. S. von Hörsten (Division of Experimental Therapeutics), we examine whether the lack or inhibition of dipeptidyl-peptidase IV (DPP4) reduces development of CKD and subsequent cardiovascular damage. In a rat model for CKD and anti-GBM-nephritis, we investigate consequences of DPP4 deficiency on disease progression and vascular as well as cardiac damage.

Funding: ELAN-Fonds; Boehringer Ingelheim GmbH

The role of PAR-2 in cardiovascular injury
PI: PD Dr. C. Daniel
Protease activated receptor-2 (PAR-2) is a G-protein coupled receptor that can be activated by numerous serine proteases which were secreted after tissue injury. In this project, we investigate PAR-2 as a potential target for the treatment of inflammatory and fibrotic organ damage. The pathogenetic role of this receptor will be evaluated using PAR-2 deficient and wildtype mice in two different animal models that are suitable to investigate inflammatory as well as pro-fibrotic changes in kidney, heart, and vessels.

Funding: Johannes and Frieda Marohn-Foundatıon

Mechanism of cardiac injury and regeneration
PI: Prof. Dr. F.B. Engel
The problem of cardiomyocyte loss following a heart injury can so far not be corrected by conventional treatment regimen. Zebrafish and newt, however, regenerate many of their organs...
including heart based on cardiomyocyte proliferation. The working group tries to identify the mechanisms that regulate cardiomyocyte proliferation during heart development and that allow the zebrafish to regenerate its heart. This knowledge will hopefully result in a therapy for heart failure patients and congenital heart disease.

**Role of the receptor GPR126 in heart development**

Pl: Prof. Dr. F.B. Engel

Having discovered that the adhesion GPCR Gpr126 plays an important role in heart development, it could be shown that Gpr126 is expressed in the endocardium. Adhesion GPCR are characterized by large N-termini and a GPS motif where they are autoproteolytically cleaved into a C-terminal and N-terminal fragment (NTF). Its deletion in mice and zebrafish resulted in markedly reduced cardiac function. Overexpression of various Gpr126 fragments suggested that NTF and CTF have independent functions. These data support a model in which endocardial cells regulate trabeculation of the heart by the binding of NTF-Gpr126 to an unknown receptor on heart muscle cells.

Funding: DFG

**Cardiac tissue engineering**

Pl: Prof. Dr. F.B. Engel

Materials for the generation of artificial heart tissue are tested for tissue replacement therapy. In close collaboration with Prof. Dr. A.R. Boccaccini (Department of Biomaterials, Faculty of Engineering), a novel blend of poly (glycerol sebacate) (PGS) and poly (butylene-co-butylene di- \-linoleate) (PBS-DLA) was tested. The addition of PBS-DLA to PGS significantly improved the mechanical properties. In addition, the material was characterized by low toxicity and good adhesion properties for heart muscle cells. Thus, it represents a promising biomaterial for cardiac tissue engineering. In addition, we began to study recombinationally produced silk as a material for cardiac tissue engineering in close collaboration with Prof. T. Scheibel (Bayreuth Materialzentrum (BayMAT), University of Bayreuth).

Funding: ELAN-Fonds, DFG

**Terminal differentiation of heart muscle cells**

Pl: Prof. Dr. F.B. Engel

Heart muscle cells of mammals differentiate and become post-mitotic. Therefore, they cannot regenerate their heart by heart muscle cell proliferation as observed in zebrafish. The group has accumulated data for a previously unknown mechanism which could explain the difference in the proliferative properties of mammalian and zebrafish heart muscle cells. In mammals, heart muscle cells lose the integrity of their centrosomes shortly after birth. This loss is coupled with the relocation of various centrosome proteins to the nuclear envelope.

Funding: EFI: CYDER

**Teaching**

The Division of Nephropathy participates in the teaching of the Institute of Pathology and acts as “Advanced Training Center for Nephropathology” of the European Society of Pathology.

Bachelor’s and Master’s theses as well as MD and PhD theses are supervised. A seminar for doctoral candidates will train the students in skills essential for their preparation.

**Selected Publications**


**International Cooperations**

- Prof. S. Shankland, Department of Nephrology, University of Washington, Seattle: USA
- Prof. M. van den Hoff, Department of Anatomy, Academic Medical Center Amsterdam, Amsterdam: The Netherlands
- Prof. L. Field, Herman B Wells Center for Pediatric Research, Indiana University, Indianapolis: USA
- Prof. D. Andersen, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense: Denmark