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
Prof. 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 therapeutic target in kidney diseases
- Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
- The role of DPP4 in crescentic glomerulonephritis
- Chronic kidney disease of unknown etiology (CKDu)
- SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
- Pathology work-up of GvL and GvHD in mice and man
- Mechanisms of cardiac injury and regeneration
- Terminal differentiation of heart muscle cells
- Role of the receptor GPR126 in heart and kidney development
- Cardiac tissue engineering

Structure of the Division

Professorships: 2
Personnel: 32
- Doctors (of Medicine): 5
- Scientists: 3 (thereof funded externally: 0)
- Graduate students: 19

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 spite of clear evidence of its importance, a basic feature of renal innervation – the regulation of sympathetic activity by afferent renal nerves – is not yet understood. It is particularly unclear whether renal afferents, i.e. the dorsal root ganglion neurons with renal projections, stimulate or inhibit sympathetic activity. We want to demonstrate in a model of experimental hypertension that afferent renal nerve activity acts rather sympathoinhibitory, but not sympathoexcitatory. This project will be done in collaboration with Prof. Dr. R. Veelken (Department of Medicine 4).

Funding: IZKF

Cell cycle control in podocytes as therapeutic target in kidney diseases

PI: Prof. 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 reenter 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: CYDER (compare own report)

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 characteristical 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 crescentic glomerulonephritis

PI: Prof. Dr. C. Daniel

In this project, we investigate the role of dipeptidyl peptidase IV (DPP4) in pathogenesis of crescentic glomerulonephritis. DPP4 is an exoprotease cleaving incretins as well as different chemokines, but can also act as an co-receptor for cell-cell recognition. Therefore we induce an anti-GBM model in rats and compare disease propagation in DPP4-inhibitor treated animals with untreated controls. Analysis will focus on the role of DPP4 in crescent formation and changes in kidney function.

Funding: Boehringer Ingelheim GmbH

SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka

PI: Prof. Dr. K. Amann

Together with nephrologists (Dr. N. Nanayakkara, Prof. Dr. K.-U. Eckardt), hydrogeologists (Prof. J. Barth, Prof. R. Chandrajith) and toxicologists (Prof. C. Zwiener) from Germany and Sri Lanka, we investigate in this interdisciplinary project causes and pathogenesis of chronic kidney disease of unknown etiology (CKDu) that is restricted to dry areas in tropical regions. Beside histopathological characterization of renal biopsies using immunohistology and electron microscopy, comprehensive analysis of drinking water will be done. The aim of this project is to uncover the causes and pathogenesis of this life-threatening disease.

Funding: BMBF

Pathology work-up of GvL and GvHD in mice and man

PI: Prof. Dr. M. Büttner-Herold

Diagnosis of GvHD is challenging due to its high variability of clinical and histopathological manifestations and insufficient validation of diagnostic criteria, even for experienced transplant pathologists. Therefore this project aims to better define diagnostic criteria of GvHD by using a round robin test with participation of four different institutes of pathology focusing on GvDH in colon. In addition, together with Prof. Dr. M. Evert (Regensburg) and Prof. Dr. A. Rosenwald (Würzburg) this project will support other subprojects of the SFB/TRR 221 (compare own re-

port) by production and evaluation of immunehistological sample analysis including human as well as murine GvDH.
Funding: DFG

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. Recently, we could demonstrate that the nuclear receptor PPAR delta is required for zebrafish heart regeneration and that its genetic as well as pharmacologic activation improves cardiac function in mice after an experimental myocardial infarct.
Funding: EFI-CYDER

Terminal differentiation of heart muscle cells

PI: 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. In addition, based on live cell imaging we have revealed the cellular mechanism that underlies the loss of proliferation resulting in binucleation and identified new marker proteins, which will help in the future to evaluate the efficiency of regenerative cardiac therapies.
Funding: EFI-CYDER, ELAN Fonds, DFG

Role of the receptor GPR126 in heart and kidney development

PI: 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 NTFGpr126 to an unknown receptor on heart muscle cells. In addition, the analysis of several Gpr126 zebrafish mutants indicates that Gpr126 plays also a role during kidney development.
Funding: DFG

Cardiac tissue engineering

PI: 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) and Prof. T. Scheibel (Bayreuth Materialzentrum, University of Bayreuth), we currently focus on the analysis of electroconductive materials and recombinantly produced silk. Our work benefits strongly from our membership in the newly funded SFB-TRR 225, which explores the fundamentals of biofabrication and its systematic exploitation with the aim and vision to generate functional human tissue models.
Funding: DFG

Teaching

The Division of Nephropathology 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

Roeder SS, Barnes TJ, Lee JS, Kato I, Eng DG, Kaverina NV, Sunseri MW, Daniel C, Amann K, Pippin JW, Shankland SJ. Activated ERK1/2 increases CD44 in glomerular parietal epithelial cells leading to matrix expansion. Kidney Int. 2017 Apr;91(4):896-913

Magadum A, Ding Y, He L, Kim T, Vasudevarao MD, Long Q, Yang K, Wickramasinghe N, Renikunta HV, Dubois N, Weidinger G, Yang Q, Engel FB. Live cell screening platform identifies PPAR? as a regulator of cardiomyocyte proliferation and cardiac repair. Cell Res. 2017; 27(8):1002-1019

Roshanbinfar K, Vogt L, Greber B, Diecke S, Boccaccini AR, Scheibel T, Engel FB. Electroconductive Biohybrid Hydrogel for Enhanced Maturation and Beating Properties of Engineered Cardiac Tissues. Adv Funct Mater. 2018; 28(42): 1803951

Leone M, Musa G, Engel FB. Cardiomyocyte binucleation is associated with aberrant mitotic microtubule distribution, mislocalization of RhoA and IQGAP3, as well as defective actomyosin ring anchorage and cleavage furrow ingression. Cardiovasc Res. 2018; 114(8):1115-1131

Pfister F, Amann K, Daniel C, Klewer M, Buttner A, Buttner-Herold M. Characteristic morphological changes in anti-VEGF therapy induced glomerular microangiopathy. Histopathology. 2018 Dec;73(6):990-1001

Prochnicki A, Amann K, Wegner M, Sock E, Pfister E, Shankland S, Pippin J, Daniel C. Characterization of Glomerular Sox9(+) Cells in Anti-Glomerular Basement Membrane Nephritis in the Rat. Am J Pathol. 2018 Nov;188(11):2529-2541

International cooperations

Prof. S. Shankland, Department of Nephrology, University of Washington, Seattle: USA

Dr. N. Nanayakkara, Kandy University Hospital, Kandy: Sri Lanka

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 C: Denmark