Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

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Research focus
- Identification and modification of hereditary kidney disease
- Pathophysiological relevance of hypoxia-inducible gene expression
- Pathogenesis of arterial hypertension and hypertensive target organ damage
- Systemic consequences of chronic kidney disease
- Acute and chronic renal allograft failure

Structure of the Department

Professorships: 5
Personnel: 231
- Doctors (of Medicine): 51
- Scientists: 13 (thereof funded externally: 11)
- Graduate students: 16

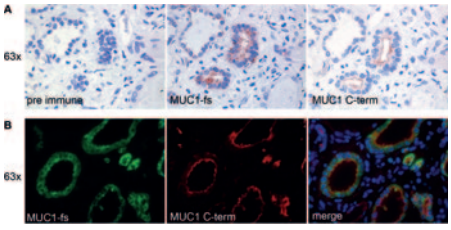
Clinical focus areas
- Diagnosis and treatment of all acute and chronic kidney diseases
- Kidney transplantation including living donor transplantation
- Sepsis and multiorgan failure
- Extracorporeal blood purification
- Refractory arterial hypertension

Research

Research at the Department of Nephrology and Hypertension has a strong translational focus. Accordingly, projects encompass experimental and patient-orientated research. Our research aims at better understanding the initiation and course of acute and chronic kidney diseases and the development and complications of arterial hypertension.
The appointment of Prof. Dr. Mario Schiffer as new director of our Department has especially strengthened our research fields "Identification and modification of hereditary kidney disease" and "Acute and chronic renal allograft failure". Furthermore, a new research focus „Proteinuric kidney diseases" will be established.

Identification and modification of hereditary kidney disease

PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, PD Dr. B. Buchholz
Recent advances in sequencing technologies permit comprehensive searches for possible genetic causes of kidney diseases, particularly in cases with a family history of the disease. Meticulous assessment of family history, pathological changes, and comorbidities is required. Experimental approaches including cell culture and zebrafish models are used to test for the functional relevance of identified genetic mutations. The ultimate aims are the improvement of diagnostic and therapeutic approaches in these kidney diseases. We developed a specific immunohistological test for one form of hereditary tubulointerstitial kidney disease.
Further work focused on one relatively frequent genetic disease, autosomal dominant polycystic kidney disease (ADPKD). Pharmacological interventions to alleviate cyst growth were tested in cell culture and mouse models. In addition, patients with ADPKD are offered participation in observational or therapeutic multicenter studies in our outpatient clinic.



Distinct biallelic expression of mucin 1 and MUC1-fs: (A) Immunohistochemical staining and (B) immunofluorescent detection of mucin 1 (C-term) and MUC1-fs in renal tubules of a patient with ADTKD-MUC1 (green, MUC1-fs; red, wild-type mucin 1)

Pathophysiological relevance of hypoxia-inducible gene expression

PI: Prof. Dr. C. Willam, PD Dr. Dr. J. Schödel, PD Dr. C. Warnecke
One pathomechanism, which is highly relevant in acute kidney failure as well as in the development of renal cell carcinoma, concerns hypoxia in kidney tissue. Focus of these studies is the regulation and functional role of the hypoxia inducible transcription factors HIF-1 and HIF-2. Based on studies of the physiological expression of these factors and their regulating enzymes, the activity of the HIF system is being investigated in different types of kidney disease. In addition, experiments are performed to test if kidney disease can be influenced by modulation of the HIF system. In addition, the epigenetic regulation of HIF transcription is being investigated in renal cell carcinoma. In parallel, the potential long term consequences of hypoxia on renal structure are being analyzed, in particular fibrogenesis, epithelial mesenchymal transition, and the growth of renal cysts.

Pathogenesis of arterial hypertension and hypertensive target organ damage

PI: Prof. Dr. R. Schmieder, Prof. Dr. J. Titze, Prof. Dr. R. Veelken, Dr. C. Kopp
A further important research area relates to studies of arterial hypertension. A specific focus in this area lies on target organ damage induced by hypertension in kidneys, heart, eye, and vasculature.
In addition, the etiology and pathogenesis of arterial hypertension are being investigated. This research includes studies on sodium homeostasis which test the hypothesis that stores of non-osmotically active sodium exist in the body and that their capacity has an important impact on blood pressure regulation. Sodium balance studies during the Mars mission project (MARS 500) and innovative imaging techniques (sodium-MRI) were used that allowed to analyze in sodium homeostasis and tissue sodium content in humans.
Additional experimental projects deal with the role of the sympathetic nervous system for the pathogenesis of hypertension and kidney injury. These studies include electrophysiological investigations of ganglion cells, measurements of tissue hormones, and studies in transgenic mice as well as tissue analyses.
Additional studies in patients are dealing with the regulation of endothelial function and in particular the influence of lipids and hormones. A special focus in recent years have been studies on the efficacy and value of renal denervation in the treatment of hypertension.

Systemic consequences of chronic kidney disease

PI: Prof. Dr. K.U. Eckardt, Prof. Dr. K.F. Hilgers
More than 10 % of the population suffer from chronic kidney disease, as defined by reduced kidney function and/or increased urinary protein excretion. Kidney disease is associated with the risk of progressive loss of renal function as well as a marked increase in cardiovascular risk. Research projects in this context deal with epidemiological questions, aspects of public health care, and the causes of an increased cardiovas-

cular risk. In order to better understand the course of chronic kidney disease and to identify novel risk factors and molecular markers, a national prospective cohort study, the GCKD study (compare own report), has been initiated. Nine regional centers and several institutes collaborate with the coordinating center in Erlangen to study 5,000 patients with chronic kidney disease and to follow them for up to ten years. These patient-centered studies are complemented by experimental investigations of mechanisms of vascular disease in rodent models of chronic kidney failure. We could show that post-ischemic angiogenesis following arterial occlusion is impaired in rats with chronic kidney disease, and that stimulation of HIF improved post-ischemic angiogenesis under these circumstances.

Acute and chronic renal allograft failure

PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, Dr. K. Heller

In cooperation with the departments of Urology and of Surgery, around 70 kidney and combined kidney-pancreas transplantations are performed per year, including living donor transplantations. Blood group incompatible living donation is a particular focus. The research program in this field aims at optimizing long term graft function. Therefore, our transplant center was included in the innovative NTX 360° project, which aims to improve long-term care of kidney transplant recipients.

In addition, multicenter trials and observational studies are being conducted to evaluate novel immunosuppressive drugs or their combination.

Teaching

The Department of Medicine 4 contributes in many ways to the teaching schedule in internal medicine, including lectures, seminars, bedside teaching in small groups, and internships. We offer electives featuring interdisciplinary teaching, focusing on vascular medicine (together with the Department of Pediatrics and Adolescent Medicine) or intensive care medicine (together with the Department of Anesthesiology). Our faculty members supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Grampp S, Schmid V, Salama R, Lauer V, Kranz F, Platt JL, Smythies J, Choudhry H, Goppelt-Struebe M, Ratcliffe PJ, Mole DR, Schödel J. Multiple renal cancer susceptibility polymorphisms modulate the HIF pathway. PLoS Genet. 2017 Jul 17; 13(7):e1006872

Schneider MP, Raff U, Kopp C, Scheppach JB, Toncar S, Wanner C, Schlieper G, Saritas T, Floege J, Schmid M, Birukov A, Dahlmann A, Linz P, Janka R, Uder M, Schmieder RE, Titze JM, Eckardt KU. Skin Sodium Concentration Correlates with Left Ventricular Hypertrophy in CKD. J Am Soc Nephrol. 2017 Jun;28(6):1867-1876

Schellinger IN, Cordasic N, Panesar J, Buchholz B, Jacobi J, Hartner A, Klanke B, Jakubiczka-Smorag J, Burzlaff N, Heinze E, Warnecke C, Raaz U, Willam C, Tsao PS, Eckardt KU, Amann K, Hilgers KF. Hypoxia inducible factor stabilization improves defective ischemia-induced angiogenesis in a rodent model of chronic kidney disease. Kidney Int. 2017 Mar;91(3):616-627

Kraus A, Peters DJM, Klanke B, Weidemann A, Willam C, Schley G, Kunzelmann K, Eckardt KU, Buchholz B. HIF-1α promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. Kidney Int. 2018 Nov;94(5):887-899

Knaup KX, Hackenbeck T, Popp B, Stoeckert J, Wenzel A, Büttner-Herold M, Pfister F, Schueler M, Seven D, May AM, Halbritter J, Gröne HJ, Reis A, Beck BB, Amann K, Ekici AB, Wiesener MS. Biallelic Expression of Mucin-1 in Autosomal Dominant Tubulointerstitial Kidney Disease: Implications for Nongenetic Disease Recognition. J Am Soc Nephrol. 2018 Sep;29(9):2298-2309

Ott C, Kopp C, Dahlmann A, Schmid A, Linz P, Cavallaro A, Hammon M, Ditting T, Veelken R, Uder M, Titze J, Schmieder RE. Impact of renal denervation on tissue Na(+) content in treatment-resistant hypertension. Clin Res Cardiol. 2018 Jan;107(1):42-48

International cooperations

Prof. R. Kleta, University College, London: UK

Prof. P.J. Ratcliffe, University of Oxford, Oxford: UK

Prof. M.D. Feldman, University of Philadelphia, Philadelphia: USA

Prof. S. Somlo, University of Yale, New Haven: USA

Prof. D. Peters, University of Leiden, Leiden: The Netherlands