UNIVERSITY HOSPITAL

Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

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

Structure of the Department

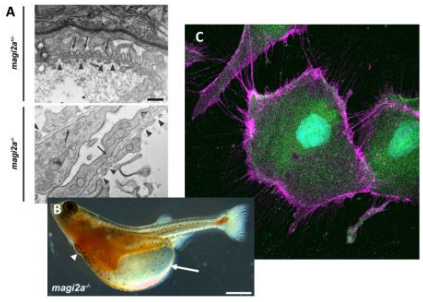
Professorships: 5
Personnel: 244
- Doctors (of Medicine): 34
- Scientists: 18 (thereof funded externally: 16)
- Graduate students: 21

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

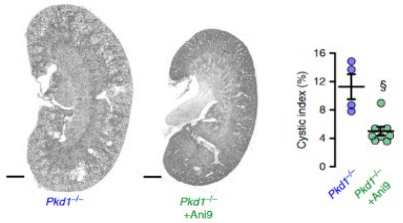
Research at the Department of Nephrology and Hypertension has a strong translational focus. Accordingly, projects encompass experimental and patient-orientated research. Our research aims at better understanding the initiation and course of acute and chronic kidney diseases and the development and complications of arterial hypertension.

Molecular mechanisms of rare kidney diseases
PI: Prof. Dr. J. Müller-Deile, Prof. Dr. M. Schiffer, Dr. Jobst-Schwan
In early 2019 we founded a center for rare disease of the kidney which cared for approximately 75 patients with rare kidney diseases in the most recent quarter. To support research on these rare kidney diseases, we also established a Research Center on Rare Kidney Diseases (RECORD), including a Clinician-Scientist program funded by the Else Kröner Fresenius foundation (www.record.fau.de). The groups working in this area of research employ cell culture models, transgenic zebrafish models, podocyte-specific knockout animals, innovative techniques, interdisciplinary cooperations and work with samples from patients with rare glomerular diseases. The projects are ultimately patient-centered. Communications between different cell types in rare kidney diseases are studied, addressing miRNAs, exosomes, autophagy mechanisms and circulating factors. The ultimate aim of this research is the identification of novel therapeutic approaches for these diseases. Conversely, a better understanding of the pathophysiology can help to prevent the use of futile therapies such as glucocorticoids in some rare, genetic forms of the nephrotic syndrome.



Magi2a knock-out zebrafish develop a primary podocytophaty displaying foot process effacement (A), and generalized edema (B). (C) MAGI2 (green) and ß-catenin (magenta) interact with each other and are colocalized in the podocyte cell membrane.

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. These approaches are brought to bear on individual cases from our outpatient clinic as well as on cases identified in a large national cohort study of patients with chronic kidney disease (GCKD study with approximately 5000 patients). The study center as well as the study's biobank is located in Erlangen. In addition, 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. In one case of a patient with kidney transplant failure we clarified the molecular pathogenesis by examining kidney tubulus cells from the patient's urine: A ciliopathy in the donor's kidney passed to the recipient was the cause of the organ's failure.
One group focuses on autosomal dominant polycystic kidney disease (ADPKD). This disease is characterized by the occurrence and subsequent progressive expansion of fluid-filled cysts in both kidneys. Expansion of the cysts over years and decades (and, consequently, the enlargement of the total volume of the kidneys) proceeds in parallel to the loss of kidney function. Mechanisms leading to cyst expansion are being investigated. Recently, one such mechanism, a chloride channel which drives chloride secretion into the cysts, was identified. Inhibitors of this channel are commercially available (albeit approved only for different diseases) any may serve as a therapeutic approach in the future.



Tubule-specific knockout of Pkd1 (Pkd1$^{-/-}$) leads to the development of polycystic kidneys. Ani9, a specific inhibitor of the calcium-activated chloride channel TMEM16A significantly reduced cyst enlargement.

Pathophysiological relevance of hypoxia-inducible gene expression
PI: Prof. Dr. C. Willam, PD Dr. Dr. J. Schödel, PD Dr. C. Warnecke, Dr. Schley, Dr. Grampp
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 genetic or pharmacological modulation of the HIF system. The focus of these studies is on the modulation of inflammation which may be either a cause or a consequence of chronic kidney disease. 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 fibrosis and epithelial to mesenchymal transition of kidney tubule cells.

Pathogenesis of arterial hypertension and hypertensive target organ damage
PI: Prof. Dr. R. Schmieder, Prof. Dr. K. Hilgers, Prof. Dr. R. Veelken, Prof. Dr. J. Titze, PD Dr. A. Dahlmann, PD Dr. A. Bosch, Dr. C. Kopp
A further important research area relates to studies of arterial hypertension. A specific focus in this area lies on the pathogenesis of hypertension as well as on target organ damage induced by hypertension in kidneys, heart, eye, and vasculature. 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. Together with the department of Radiology, innovative imaging techniques (sodium-MRI) were established and utilized to analyze 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 and vice versa: an important focus of this research is the role of afferent nerve fibers, which transmit signals from kidney tissue to the brain for the regulation of sympathetic nervous activity. These studies include electrophysiological investigations of ganglion cells, direct recordings of both afferent and efferent fibers in animals, as well as studying the response of patients to renal denervation.
From a patient-centered perspective, target organ damage of the heart, the kidneys and the blood vessels should be considered in conjunction with other risk factors, which often cluster together with hypertension, especially diabetes, hyperlipidemia, and chronic kidney disease. Research on the mechanisms of target organ damage are the focus of experimental as well as clinical studies, the latter taking advantage of data and samples from the aforementioned national cohort study GCKD.

Acute and chronic renal allograft failure
PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, Dr. K. Heller, Dr. M. Opgenoorth
In cooperation with the departments of Urology and of Surgery, around 65 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 follow-up project NTX 360° which aims to improve long-term maintenance care of kidney transplant recipients. In addition, multicenter trials and observational studies are being conducted to evaluate novel immune-suppressive drugs or their combination. To counter severe Virus infections (CMV and BKV) complicating the post-transplant care, we started the generation, amplification and application of autologous or allogenic virus-specific T-cells, together with the department of medicine 5.

Fit on the waiting list – a rehabilitation program for patients on dialysis
PI: Prof. Dr. M. Schiffer, Dr. K. Heller, Dr. M. Opgenoorth
This clinical research program funded by the Bayerisches Staatsministerium für Gesundheit und Pflege is a cooperation between our Department of Medicine 4, the M&I – rehabilitation clinics in Herzogenaurach and Bad Heilbrunn and the Gesundheitsregion PLUS Erlangen-Höchstadt. The aim of the project is a sustained improvement of the care for elderly patients on dialysis who are listed for kidney transplantation. These patients are especially vulnerable to develop a rapid deterioration of their physical and mental health. To alleviate this problem, individual rehabilitation plans targeted to the particular health problems (and scheduling problems) of dialysis patients are provided and implemented. Office-based nephron-logists cooperating with our clinic recruit patients participating in this program. The rehabilitation measures are intended to maintain and improve the patients' health status, and to render the participants viable candidates for transplantation (https://www.fit-für-transplantation.fau.de).

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).
In 2020, many on-line learning modules were developed as a "replacement" for lectures, seminars and practical courses, which could not be held in presence due to the corona pandemic.
Our faculty members supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Müller-Deile J, Schenk H, Schroder P, Schulze K, Bolaños-Palmieri P, Siegerist F, Endlich N, Haller H, Schiffer M. Circulating factors cause proteinuria in parabiotic zebrafish. Kidney Int. 2019; 96:342-349

Jobst-Schwan T, Hoogstraten CA, Kolvenbach CM, Schmidt JM, Kolb A, Eddy K, Schneider R, Ashraf S, Widmeier E, Majmundar AJ, Hildebrandt F. Corticosteroid treatment exacerbates nephrotic syndrome in a zebrafish model of magi2a knockout. Kidney Int. 2019; 95:1079-1090

Schley G, Klanke B, Kalucka J, Schatz V, Daniel C, Mayer M, Goppelt-Struebe M, Herrmann M, Thorsteinsdottir M, Palsson R, Beneke A, Katschinski DM, Burzlaff N, Eckardt KU, Weidemann A, Jantsch J, Willam C. Mononuclear phagocytes orchestrate prolyl hydroxylase inhibition-mediated renoprotection in chronic tubulointerstitial nephritis. Kidney Int. 2019; 96:378-396

Schödel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. Nat Rev Nephrol. 2019; 15:641-659

Tossidou I, Teng B, Worthmann K, Müller-Deile J, Jobst-Schwan T, Kardinal C, Schroder P, Bolanos-Palmieri P, Haller H, Willerding J, Drost DM, de Jonge L, Reubold T, Eschenburg S, Johnson RI, Schiffer M. Tyrosine Phosphorylation of CD2AP Affects Stability of the Slit Diaphragm Complex. J Am Soc Nephrol. 2019; 30:1220-1237

Cabrita I, Kraus A, Scholz JK, Skoczynski K, Schreiber R, Kunzelmann K, Buchholz B: Cyst growth in ADPKD is prevented by pharmacological and genetic inhibition of TMEM16A in vivo. Nat Commun. 2020; 11: 4320

Rodionova K, Veelken R, Hilgers KF, Paulus EM, Linz P, Fischer MJM, Schenker M, Reeh P, Tiegs G, Ott C, Schmieder R, Schiffer M, Amann K, Ditting T. Afferent renal innervation in anti-Thy1.1 nephritis in rats. Am J Physiol Renal Physiol. 2020; 319:F822-F832

Wiesener A, Knaup KX, Büttner-Herold M, Dieterle A, Stoeckert J, Riedl B , Morath C, Wald A, Vondran F, Braun F, Schödel J, Schueler M, Schiffer M, Amann K, Reis A, Kraus C, Wiesener MS. Molecular diagnosis of kidney transplant failure based on urine. Am J Transplant. 2020; 20: 1410 – 1416

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

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

Prof. F. Hildebrandt, Harvard University, Cambridge: USA