Head of Research Unit:
Title, Name: Univ. Prof. Dr. Gert Mayer

Contact:
Address: Department of Internal Medicine IV (Nephrology and Hypertension)
         Anichstrasse 35; 6020 Innsbruck; Austria
Email: gert.mayer@i-med.ac.at
Phone: 0512 504-25855
Fax: 0512 504-25857
Web: www.nephrologie-innsbruck.at
Keywords:
chronic kidney disease; pathophysiology; systems biology; stratified/personalized medicine; epidemiology; autoimmune disease; hemodialysis; cardiovascular mortality; renal transplantation

Research Focus of the Research Unit:
In order to better characterize patho-physiologically complex phenotypes such as chronic kidney disease we apply modern epidemiology and “Omics”-techniques in conjunction with state of the art systems biology approaches to derive predictive biomarkers to implement innovative stratified/personalized treatment. This translational research focus is supported by experimental and clinical studies in selected populations and by strong national and international collaborations.

General Facts about Aims and Structure of the Research Unit:
The Department is the tertiary referral center for patients with renal disease (native kidney, renal replacement therapy, kidney transplantation) and hypertension for the Western part of Austria and Southern Tyrol. Specialised outpatients as well as inpatients facilities and a state of the art unit for extra-corporeal therapy (hemo- as well as peritoneal dialysis, plasmapheresis, liver support therapy, immunoabsorption) allow serving a large clinical population and this background drives our translational research efforts. The laboratories of the Department hold a clinical routine as well as a molecular biology (including microarray facility) and cell culture unit. Our clinical trial core unit manages investigator driven projects as well as the participation in large multicenter clinical trials and a large bio-banking effort. The common denominator of the Department’s research activity is the area of personalized medicine in the various aspects of Nephrology and we collaborate with multiple academic and industry partners in national and/or EU funded projects (EMERGENTEC biodevelopment Vienna, AbbVie, TEVA, University of Vienna, University of Groningen, STENO Diabetes Center, University of Glasgow, Semmelweis University, University of Silesia, University Erlangen, Charite Berlin, Stanford University etc.). During our recent activities we focused primarily on the application of systems-biology techniques within the FP 7 funded project SysKid (www.syskid.eu), to which our Department was one of the main contributors. In the next years this focus will be developed within the IMI project BEAT-DKD

Research (2013 - 2016):
Basic research activities
Cellular and molecular nephrology
Lead: Univ. Prof. Dr. Herbert Schramek

Diabetes mellitus (DM) is a major and growing health problem worldwide. Normalizing hyperglycemia is not only crucial for slowing progression of the disease process but also for preventing secondary consequences such as diabetic nephropathy. Sodium glucose cotransporters SGLT2 and SGLT1 in the apical membrane of the proximal tubule have been established as the primary mechanisms of glucose reabsorption in the kidney. Inhibitors of SGLT2 have recently been approved as new antihyperglycemic drugs in type 2 DM. Although studies in mice have shown that pharmacological SGLT2 inhibition itself increases renal SGLT2 protein expression, little is known about the regulation of proximal tubular
glucose transporter expression. Thus, our lab is interested in the effects of pharmacologic inhibitors of sodium glucose cotransporters on differential genes expression in human proximal tubular cells (PTCs). Identifying novel genes regulated by these antihyperglycemic drugs along the proximal tubule will lead to a better understanding of their action and the underlying mechanisms in vivo.

Renal fibrosis is the final, common pathway of many kidney diseases leading to nephron loss. The pathophysiological mechanisms include tubular cell injury, infiltration of inflammatory cells, accumulation of (myo)-fibroblasts, and rarefaction of the peritubular microvasculature. Of all the cell types involved, proximal tubular epithelial cells (PTCs) play a central role. Thus, the laboratory is also interested in the function of this specific cell type during tubulointerstitial injury and fibrogenesis.

Utilizing pro-inflammatory and pro-fibrotic ligands such as IL-1β, TNF-α, and TGF-β1 we do not only investigate novel molecular mechanisms, which are associated with cellular injury leading to an activated, dedifferentiated PTC phenotype but also those, which induce cell protection or repair.

Distinct human PTC lines have been used to investigate expression and regulation of several pro-inflammatory and pro-fibrotic genes including CCL2 and CTGF, respectively (figure 1). We recently discovered that oncostatin M (OSM) is able to stimulate acute inflammation via its synergistic effects with other pro-inflammatory cytokines early after injury, but may attenuate chronic inflammation and fibrogenesis at later time points. Additional gene silencing approaches identified some of the intracellular signalling pathways involved. Future goals include the functional analysis of novel genes of interest regulating PTC phenotype during PTC injury, inflammation and progressive renal fibrosis.

Translational research activities
Transcriptional profiling and systems biology application in chronic renal disease
Lead: Johannes Leierer PhD, Gert Mayer MD

Several years ago we established (in collaboration with the University of Stanford/California) microarray technology to study whole organ and, via application of laser capture micro-dissection, renal compartment specific differential mRNA and miRNA expression in human and animal tissue. When compared to normal controls tubular cells from patients with proteinuric nephropathies revealed significant transcriptional de-regulation of pro-fibrotic but also tubulo-protective (e.g. BMP-7) mechanisms. When compared to patients with stable renal disease patients with progressive renal failure showed an attenuated tubular VEGF-A expression despite a strong hypoxia signal (see figure 2). These gene expression profiles also helped to define new, clinically relevant biomarkers. Doz. Dr. Michael Rudnicki, a member of our group, has recently started to focus on simultaneous analysis of renal miRNA and mRNA profiles. His work revealed regulatory networks, in which specific miRNAs activate entire signal transduction pathways such as inflammation or apoptosis.

Recently transcriptomics data were complemented by proteomic, metabolomic and genomic profiles in the large, multinational EU FP-7 funded project SysKid (Systems Biology towards Novel Chronic Kidney Disease; www.syskid.eu). In collaboration with EMERGENTEC biodevelopment and the Medical Universities of Vienna and Groningen we developed a proprietary systems biology derived molecular model of renal disease in type II diabetes and identified molecular processes associated with progressive renal function loss. Biomarkers associated with these pathways were discovered and validated in large patient cohorts. Currently we are working to match the disease specific molecular profiles with drug mode of action molecular profiles to gain access to targeted therapy (figure 3). This approach will be advanced in the IMI project BEAT-DKD, which will start late 2016 and coordinate the
efforts of many academic centers from around the world and pharmaceutical industry and in the Austrian TOPVAS study, which recruits patients after renal transplantation and dissects the effects of ageing on transcriptional profiles in the kidney and calcineurin inhibitor toxicity. Ass. Prof. Dr. Dr. Hannes Neuwirt, another team member, is working on biomarkers that predict long term graft function and is also interested in the role of the complement system in kidney transplant models. Additionally he is exploring alternative dialysis modalities, such as electro-osmosis in collaboration with Prof. Thomas Bechtold (Research Institute of Textile Chemistry and Textile Physics University).

In order to validate our “in silico” derived hypotheses on predictive biomarkers we are also leading several large scale, national and multinational prospective cohort studies (e.g. The Austrian Dialysis and Transplant Registry; PROVALID, a study in >4.000 patients with type 2 diabetes in 5 European countries; TOPVAS including >240 patients after renal transplantation in Austria). The data collected there form the basis for outcomes and health economics research on a European level. Dr. Julia Kerschbaum, MSc, a further member of our team, is working on prediction models for adverse events in patients with chronic kidney disease. In particular, she is interested in the prediction of cardiovascular events and kidney failure in patients with type II diabetes. Furthermore, she is working on general epidemiological issues in order to identify factors which might improve prognosis in our patients.

Clinical research activities

Targeted therapy in renal disease

Lead: Doz. Dr. Rudnicki (peritoneal dialysis, anti CD20, Mb. Fabry), Dr. Markus Pirklbauer (cardiovascular mortality on hemodialysis); Dr. Andreas Kronbichler (autoimmune diseases)

Peritonitis is the most serious complication in patients on peritoneal dialysis (PD). In an analysis of PD patients treated locally and in a multicenter national study Dr. Julia Kerschbaum and Doz. Dr. Michael Rudnicki identified factors associated with risk of peritonitis. Interestingly oral active vitamin D therapy was associated with a decreased incidence and improved survival.

In collaboration with the Department of Nephrology, Ospedali Riuniti di Bergamo/Italy, we examined the effect of an anti CD20 antibody in frequently relapsing nephrotic diseases in children and in adults. Based on data obtained in a prospective study and a review we were able to show that this approach is a valuable therapeutic option.

In collaboration with the Department for Pediatrics we treat and recruited patients with rare diseases, in particular Fabry’s disease, into a European multicenter study on enzyme replacement therapy.

Regarding the excessive cardiovascular mortality in patients with end stage renal disease we are interested in the possible detrimental effect of positive calcium mass balance during hemodialysis. We propose that a disturbance in the rapidly accessible bone calcium pool in chronic renal disease diminishes the capacity to buffer a calcium load, by this contributing to vascular calcification.

The kidney is often affected by autoimmune disorders. Our research aim is delineating pathogenetic steps in nephrotic syndrome, anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis and systemic lupus erythematosus (SLE). In a recent publication, we aimed to corroborate differentially expressed biomarkers and proposed a panel of C-reactive protein and MCP-1 in renal vasculitis. We
are currently working on a proteomics approach using a novel method (SWATH-MS) which may help to identify novel candidates in proteinase 3 (PR3)-positive vasculitis (supported by Addenbrooke’s Charitable Trust). Moreover, we aim to delineate the connection between autoimmunity and the human microbiome. Staphylococcus aureus may directly be involved in the ethiopathogenesis of granulomatosis with polyangiitis (GPA). We are currently working on two projects, one supported by NIHR and one by Arthritis Research UK, to prove whether colonization with Staphylococcus aureus is secondary to vasculitis or coincide with the onset/relapse of the disease.

Thus, the future aims are to combine clinical findings with an experimental setting to increase the understanding of these diseases. These efforts are driven forwards via a collaboration with Dr. David Jayne (Cambridge University Hospitals, UK). From a clinical perspective, we are mainly interested in complications of immunosuppressive treatment, i.e. infectious complications, malignancy and venous thromboembolic events. Clearly, the future aim will be a combination of these events with a mechanistic approach potentially displaying patients at risk to develop such complications. This effort is driven via collaborations within the European Vasculitis Society. In addition, the research group will participate in several clinical trials and is currently co-investigator in a European trial aiming to investigate the role of extracorporeal treatment (IAS) in refractory SLE (Figure 4).
Figure 1.

Copyright: Herbert Schramek
Text: Alterations of proximal tubular cell (PTC) phenotype and gene expression in response to tubular injury.
Integrative systems biology analysis of renal gene expression data shows differential regulation of hypoxia and angiogenesis pathways in stable and progressive kidney diseases.
Figure 3.

Copyright: Gert Mayer

Text: Interference of a drug mechanism of action molecular model (left) with the diabetic nephropathy phenotype molecular model (right). Interfering processes on the drug (blue) and phenotype side (red) are indicated.
Figure 4.

Copyright: Autoimmunity Reviews

Text: Technical aspects and molecular changes exerted by immunoabsorption (left side) and plasma exchange (right side) in systemic lupus erythematosus.
Selected Publications


- Selection of Acquired Funding in 2013/14
SYSKID - Systems biology towards novel chronic kidney disease diagnosis and treatment
EU - FP7 Gert Mayer

PROVALID – Multi-centre study regarding the cumulative incidence of renal outcomes in patients with type II diabetes in different European countries
AbbVie research fund Gert Mayer

TOPVAS - The Transplant Outcome Prediction Validation Study
TEVA research grant fund Gert Mayer

Hämoelektroosmose
Austria Wirtschaftsservice Ges.m.b.H. Hannes Neuwirt

Der labile Kalziumpool und seine Bedeutung für das kardiovaskuläre Risiko in Hämodialysepatienten OENB Markus Pirklbauer
Collaborations outside MUI

- Bernd Mayer, EMERGENTEC biodevelopment GmbH; Vienna, Austria
- Rainer Oberbauer, Division of Nephrology and Dialysis; Medical University Vienna
- Harald Mischak, Mosaiques Diagnostics GmbH; Hannover, Germany
- Peter Rossing, STENO Diabetes Center; Gentofte, Denmark
- Johannes Mann, Universität Erlangen; Erlangen, Germany
- Dick de Zeeuw, Hiddo Lambers Heerspink, Academisch Ziekenhuis; Groningen, The Netherlands
- Andrzej Wiecek, Słaski Uniwersytet Medyczny Katowice; Katowice, Poland
- Laszlo Rosivall, Semmelweis University; Budapest, Hungary
- Patrick Mark, University of Glasgow; Glasgow, UK
- Kitty Jager, Academisch Medisch Centrum bij de Universiteit van Amsterdam; Amsterdam, The Netherlands
- Mariano Rodriguez, Universidad de Cordoba; Cordoba, Spain
- Timothy Meyer, Stanford University School of Medicine; California, USA
- David Jayne, Vasculitis and Lupus Clinic, Cambridge University Hospitals; United Kingdom
- Luis Quintana, Servicio de Nefrología y Trasplante Renal, Universidad de Barcelona; Barcelona, Spain
- Daiki Nakagomi, Department of Allergy and Clinical Immunology, Chiba University; Chiba, Japan
- Jae Il Shin, Department of Pediatric Nephrology, Yonsei University College of Medicine, Severance Children’s Hospital; Seoul, Korea
- Giuseppe Remuzzi and Piero Ruggenenti, Department of Nephrology, Ospedali Riuniti di Bergamo/Italy
- Andreas Pasch, University Hospital for Nephrology and Hypertension, Inselspital Bern; Bern, Switzerland
- Zoltan Prohaszka, Semmelweis University, Dept. of Internal Medicine III, Budapest, Hungary