# Research Report MUI 2016
## Input Form

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### 1. Name of Research Unit:
Department of Internal Medicine IV (Nephrology and Hypertension)

### 2. Head of Research Unit:

| | |
|---|---|
| Title, Name: | Univ. Prof. Dr. Gert Mayer |
| Photo, Filename: | G.Mayer |
| Photo, Copyright (e.g. MUI, private, Name): | private |

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### 4. Extended Version

4 Pages

### 5. Keywords:

chronic kidney disease; pathophysiology; systems biology; stratified/personalized medicine; epidemiology; autoimmune disease; hemodialysis; cardiovascular mortality; renal transplantation

### 6. Research Focus of the Research Unit:

In order to better characterize pathophysiologically 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 prognostic and 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.

## 7. General Facts about Aims and Structure of the Research Unit

The Department is the tertiary referral centre for patients with acute and chronic renal diseases (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, immune-adsorption) 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 multicentre clinical trials and a large bio-banking effort. The most recent effort is to relocate the „Austrian Dialysis and Transplantation Registry“ to Innsbruck in collaboration with the Department of Statistics, Informatics and Health Economy. 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 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. Last year a successor project (Beat-DKD) was funded by the Innovative Medicine Initiative. Beat-DKD again is a large consortium project with 28 academic and industry partners and next to WP lead functions our Department is involved in various research activities (figure 1).

## 7. Branch of science subject to OESTAT classification:

3526 Nephrologie

## 8. Research (2015 - 2016)

**Basic research activities**

**Cellular and molecular nephrology**

Lead: Herbert Schramek MD, Markus Pirklbauer MD

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 and although expression of SGLT2 mRNA and protein is increased in renal biopsies from human subjects with diabetic nephropathy, there is very limited data in the literature about the regulation of sodium gradient dependent glucose transporter expression. The lab is currently studying the effects of pharmacological inhibitors of sodium glucose cotransporters on gene expression in human proximal tubular cells. Utilizing two SGLT2 inhibitors, namely Empagliflocin and Canagliflocin, we investigate

their effects on SGLT2 and GLUT2 expression in the presence and in the absence of pro-inflammatory and pro-fibrotic ligands such as IL-1β and TGF-β1. Additional study endpoints are the expression of TSP-1, CTGF, CCL2, CCL5, and IL-6. In a second ongoing experimental approach, cDNA microarray analysis is performed in the two independent proximal tubular cell lines RPTEC/TERT1 and HK-2 exposed either to Empagliflocin or Canagliflocin when compared with untreated control cells. One of several interesting preliminary results of these studies is shown in figure 2.

**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, Doz. Dr. Michael Rudnicki focuses on respective combined data analysis. In collaboration with the Mario Negri Institute (Bergamo/Italy) we were able to identify and characterize a novel miRNA (miR-184) as a downstream effector of albuminuria, which drives renal fibrosis in a rat model of diabetic nephropathy. Further miRNAs are being studied as serum biomarkers to distinguish diabetic from non-diabetic renal diseases.

Recently in house generated 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). In collaboration with EMERGENTEC biodevelopment and the Medical Universities of Vienna and Groningen we developed a systems biology derived molecular model of renal disease in type II diabetes and identified molecular processes associated with progressive renal function loss. Biomarkers reflecting 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. This approach will be put forward in the IMI project BEAT-DKD, which started late 2016 and coordinates the efforts of many academic centres 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. 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 with (e.g. PROVALID, a study in 4.000 patients with type 2 diabetes in 5 European countries; TOPVAS including 240 patients after renal transplantation in Austria) or without bio-banking (Austria Dialysis and Transplant Registry). The data collected there form the basis for outcomes and health economics research on a European level.

Assoc. Prof. Dr. Hannes Neuwirt, another team member, is working on biomarkers that predict long term graft function and the role of the complement system in kidney transplant models. A further clinical research focus is on ABO incompatible renal transplantation. Additionally Dr. Neuwirt is exploring alternative dialysis modalities, such as electro-osmosis in collaboration with Prof. Thomas Bechtold (Research Institute of Textile Chemistry and Textile Physics University).

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 and she is a main contributor to the "Austrian Dialysis and Transplantation" registry transfer.

**Clinical research activities**

**Targeted therapy in renal disease**

Lead: Michael Rudnicki MD (peritoneal dialysis, anti CD20, rare diseases such as ADPKD or Mb. Fabry, live kidney donation), Markus Pirklbauer MD (cardiovascular mortality on hemodialysis); Andreas Kronbichler MD (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 multicentre national study Julia Kerschbaum and 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 multicentre study on enzyme replacement therapy. We also participate in national and international studies on the safety of the ADH antagonist Tolvaptan for treatment of autosomal-dominant polycystic kidney diseases.

Live kidney donation is the optimal treatment for patients with end-stage renal disease, but data on the risks for the donors are controversially discussed. In a close collaboration with the Department of Visceral, Transplant and Thoracic Surgery we evaluated the long-term clinical course of live kidney donors who donated their kidney in Innsbruck between 1985 and 2015. The risks of chronic kidney and cardiovascular disease have been quantified, and risk factors have been identified, which are now being used for risk stratification of future kidney donors. In addition we currently evaluate the impact of donor characteristics on the graft function of the recipient.

Regarding the excessive cardiovascular mortality in patients with end stage renal disease Markus Pirklbauer investigates the possible detrimental effect of positive calcium mass balance during hemodialysis. Supported by an educational research grant provided by the Austrian National Bank we recently published first experimental evidence for the existence of a rapidly exchangeable calcium pool counteracting acute deviations of extracellular calcium concentration in hemodialysis patients and for the involvement of bone in acute extracellular calcium regulation in vivo. Based on the promising results of our acute calcium kinetics studies we are currently establishing a research-collaboration with the Renal Research Institute New York (Head: Prof. Peter Kotanko).
The kidney is often affected by autoimmune disorders. Our research aim is delineating pathogenetic steps in nephrotic syndrome (figure 3), anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (figure 4) and systemic lupus erythematosus (SLE). 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 etiopathogenesis 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 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.

## 9. Pictures:

Please attach figures as separate files, not more than three.
Format: tif, eps or jpg
Resolution: Photographs at least 300 dpi, line graphs and illustrations preferably in eps format with at least 600 dpi.

Copyright: **If the picture is already published: Name of journal**
Otherwise blank or name of person who took picture, made figure or graph**.**

**Figure Nr. 1:**

Filename: 1

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Text for figure: The workpackage structure of Beat-DKD

**Figure Nr. 2:**

Filename: 2

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Text: The effect of SGLT-2 inhibitors and cytokines on SGLT-2 mRNA expression levels in the proximal tubular cell line RPTEC/TERT1

**Figure Nr. 3:**

Filename: 3

Copyright: Kronichler A et al. J Immunol Res. 2016;2016:2068691. doi: 10.1155/2016/2068691. Epub 2016 Jul 18

Text: JPEG holds text to figure

**Extended Version only (4 pages):**

**Figure Nr. 4:**

Filename: 4

Copyright: private

Text: JPEG holds text to figure

## 10. Selected Publications

Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis
van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, Jayne DR, Bajema IM, Rahmattulla C
ANN RHEUM DIS: 2016; doi: 10.1136/annrheumdis-2016-209925

Systems Biology-Derived Biomarkers to Predict Progression of Renal Function Decline in Type 2 Diabetes
Mayer G, Heerspink HJ, Aschauer C, Heinzel A, Heinze G, Kainz A, Sunzenauer J, Perco P, de Zeeuw D, Rossing P, Pena M, Oberbauer R; SYSKID Consortium..
DIABETES CARE 2017;40:391-397

International Network of Chronic Kidney Disease cohort studies (iNET-CKD): a global network of chronic kidney disease cohorts
Dienemann T, Fujii N, Orlandi P, Nessel L, Furth SL, Hoy WE, Matsuo S, Mayer G, Methven S, Schaefer F, Schaeffner ES, Solá L, Stengel B, Wanner C, Zhang L, Levin A, Eckardt KU, Feldman HI.
BMC NEPHROL 2016 doi: 10.1186/s12882-016-0335-2

Acute calcium kinetics in haemodialysis patients
Pirklbauer M, Schupart R, Mayer G
EUR J CLIN INVEST 2016;46:976-984

Rudnicki M, Perco P, D´haene B, Leierer J, Heinzel A, Mühlberger I, Schweibert N, Sunzenauer J, Regele H, Kronbichler A, Mestdagh P, Vandesompele J, Mayer B, Mayer G. Renal microRNA- and RNA-profiles in progressive chronic kidney disease.
EUR J CLIN INVEST 2016;46:213-26

## 11. Selection of Acquired Funding in 2015/16

Beat-DKD; Innovative Medicines Initiative; Gert Mayer
Hämoelektroosmose; Austria Wirtschaftsservice Ges.m.b.H. ; Hannes Neuwirt
Arthitis Research UK Microbiome Pathfinder Award; Andreas Kronbhcler

## 12. 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
- Dick de Zeeuw, Hiddo Lambers Heerspink, Academisch Ziekenhuis; Groningen, The Netherlands
- Andrzej Wiecek, Slaski Uniwersytet Medyczny Katowicach; Kattowice, Poland
- Laszlo Rosivall, Semmelweis University; Budapest, Hungary
- Patrick Mark, University of Glasgow; Glasgow, UK
- Timothy Meyer, Stanford University School of Medicine; California, USA
- David Jayne, Vasculitis and Lupus Clinic, Cambridge University Hospitals; United Kingdom
- Annette Bruchfeld, Division of Renal Medicine, Karolinska Institutet; Stockholm, Sweden
- Daiki Nakagomi, Department of Allergy and Clinical Immunology, Chiba University; Chiba, Japan
- Thomas Neumann, Department of Internal Medicine III, Jena University Hospital; Jena, Germany
- Jae Il Shin, Department of Pediatric Nephrology, Yonsei University College of Medicine, Severance Children's Hospital; Seoul, Korea
- Piero Ruggenenti, Department of Nephrology, Ospedali Riuniti di Bergamo/Italy
- Peter Kotanko, Renal Research Institute, Mt Sinai Medical Center, New York, USA
- Mathias Kretzler, Ann Arbour University Michigan, USA

## 13. Corefacilities

## 14. Permission to Publish

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x yes ☐ no