**Project title:**
The Cardiovascular Morbidity in Children with Chronic Kidney Disease (4C) Study

**Length of the project:**
From June 1st 2010 to May 31 2017 (end of funding, the Study continued till December 2018)

**Principal Investigator:**
Franz Schaefer

**Proposed research:**
While most patients with childhood-onset chronic kidney disease (CKD) nowadays survive into adulthood, their cardiovascular (CV) morbidity and mortality at young adult age is excessive due to extensive cumulative exposure to non-traditional CV risk factors associated with uremia. Therefore, the prevention, diagnosis and treatment of early CV disease is becoming a primary objective of pediatric CKD management. While early CV disease has been observed in children with even moderate CKD, the causative factors and natural evolution of CV morbidity and their relationship to CKD progression are incompletely understood due to a lack of prospective studies.

Due to the absence of vascular pathology secondary to ageing, diabetes and smoking, the pediatric CKD population should permit a uniquely sensitive assessment of associations between early CV lesions and biochemical and genetic risk factors.

The ESCAPE Network, a consortium of pediatric nephrology centers in 13 European countries, has previously generated fundamental information about CV abnormalities in pediatric CKD. Building on this expertise, the Network is launching the Cardiovascular Comorbidity in Children with CKD (4C) Study, a long-term observational study exploring the prevalence, extent and progression of CV pathology and its association with CKD progression.

The morphology and function of the heart and large arteries will be monitored by sensitive non-invasive methods in 700 children aged 6-17 years with eGFR 10-45 ml/min/1.73m². Age-specific reference cohorts will be studied in parallel. Arterial biopsies obtained on occasion of access or transplant surgery will be characterized pathoanatomically and pathochemically. Multiple potential clinical, anthropometric, biochemical and pharmacological risk factors will be monitored and related to the evolution of CV status. A genome-wide association study will be performed to identify common genetic variants associated with CV disease and/or CKD progression.

Monitoring will be continued when ESRD is reached to study effects of different renal replacement therapy modalities.

**Aim of the research:**
The 4C Study is an observational longitudinal study in children and adolescents with advanced chronic kidney disease designed to address the following research topics:

- Distribution of indices of large artery morphology (carotid intima media thickness, cIMT) and function (aortic pulse wave velocity, PWV) in healthy children
- Prevalence of left ventricular hypertrophy (LV mass index) and myocardial dysfunction (cardiac strain) in children with CKD
- Prevalence of abnormal large artery morphology (cIMT) and function (PWV) in children with CKD
- Change of cardiac and arterial morphological and functional abnormalities during CKD progression
- Impact of dialysis and transplantation on cardiac and arterial pathology in children with end-stage renal disease
- Impact of conventional, uremia- and dialysis-associated risk factors on cardiac and arterial abnormalities in children and adolescents
- Predictive value of established and novel serum and urine biomarkers for cardiac and vascular abnormalities in children with CKD
- Association of common genetic variants with progression of CKD and cardiovascular disease in children and adolescents with CKD (genome wide association study)
- Impact of uremia and dialysis on arterial tissue morphology, gene and protein expression in children with end-stage renal disease
List of the papers published in peer reviewed journals:


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**List of presentations at major congresses/meetings:**

**German Society for Pediatric Nephrology 2010**

**European Academy for Pediatric Societies (EAPS) 2010**

**Turkish Society of Pediatric Nephrology, Annual Meeting 2010**
- Doyon A et al. Oscillometric measurement of aortal pulse wave velocity in children.

**International Pediatric Nephrology Association (IPNA) 2010**

**ASN 2010**

**German Society for Pediatric Nephrology 2011**

**ESPN 2011**

**European Society of Hypertension, 21st Meeting on Hypertension and Cardiovascular Prevention 2011**

**ESPN 2012**

**Annual Meeting of the German Society of Pediatric Nephrology 2012**

**American Transplant Congress 2013**
- Melk A et al. Cardiovascular Risk Profile in Children after Renal Transplantation - Introducing the 4C-T Sub-Study.

**EDTA 2013**
- Schaefer B, Macher-Goeppinger S, Bayazit AK, Sallay P, Holland-Cunz S, Querfeld U, Warady BA, Schaefer F, Schmitt CP. First results from the International Pediatric Peritoneal Biopsy Study

**IPNA 2013**
- Doyon et al. Impact of recombinant growth hormone (rGH) therapy on bone metabolism in children with chronic kidney disease (CKD): Findings from the 4C Study
- Matteucci CM et al. Advanced Parameters of Cardiac Mechanics in Children with Chronic Kidney Disease: A Preliminary Report From the 4C Study
- Melk A et al. Cardiovascular Comorbidity in Children after Renal Transplantation – First Results from the 4C-T Study

**ASN 2013**
- Doyon A et al. Serum hepcidin is a superior indicator of functional iron status in children with chronic kidney disease.

**ESPN 2014**
- Duzova A et al. Prevalence and evolution of ambulatory hypertension in children with CKD: Results from the 4C Study
- Duzova A et al. Arterial ambulatory stiffness index and blood pressure variability in healthy children and adolescents
- Wühl E et al. and the ESCAPE/4C Study Consortium: UMOD genotype, renal diagnosis, GFR, and gender determine uromodulin excretion in children with chronic kidney disease (CKD)

**ASN 2014**
- Wühl E et al. Uromodulin excretion predicts renal disease progression in children with chronic kidney disease (CKD)
- Doyon et al. Genetic, Environmental and Disease-Associated Determinants of Vitamin D Status in Children with Chronic Kidney Disease: Findings from the 4C Study.
- Wuttke et al. Baseline GWAS Results in the PediGFR Cohort: Six Novel Loci Associate with Estimated GFR and proteinuria.

**American Transplant Congress 2015**
- Melk, D. Thurn-Valsassina, B. Schmidt, A. Duzova, B. Soezeri, A. Bayazit, S. Caliskan, U. Querfeld, K. Ažukaitis, E. Wuehl, F. Schaefer. Longitudinal Follow-Up of Cardiovascular Comorbidity in Pediatric Renal Transplant Recipients – Results from the 4C-T Study

**25th European Meeting on Hypertension and Cardiovascular Protection, 2015**


Uremia and PD-induced transformation of peritoneal membrane vasculature – findings from the International Pediatric PD Biobank.


**GPN 2016**


**International Atherosclerosis Society 2015**

- Uwe Querfeld, Anke Doyon, Elke Wühl, Daniela Thurn-Valsassina, Mieczyslaw Litwin, Aysun Bayazit, Ali Duzova, Mahmoud Civilbal, Bethül Sözeri, Franz Schaefer. The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study: baseline data of a multicentre prospective observational study

**IPNA 2016**


**ASN 2016**


**IPNA International Workshop for Clinical and Epidemiological Research in Pediatric Nephrology 2017**

- Querfeld U. Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study.


Hospitalization Burden In Children With Chronic Kidney Disease (CKD): Findings From The 4C Study.

Causes Of Non-Elective Hospitalizations In Children With Chronic Kidney Disease (CKD): Findings From The 4C Study.

Impaired Systolic and Diastolic Left Ventricular Function in Children with Chronic Kidney Disease – Results from the 4C Study.