



How to fly  
without wings

—  
from flies to  
Chronic Kidney  
Disease



Danilo Fliser

Univ.-Prof. & Director

Saarland University Medical Centre

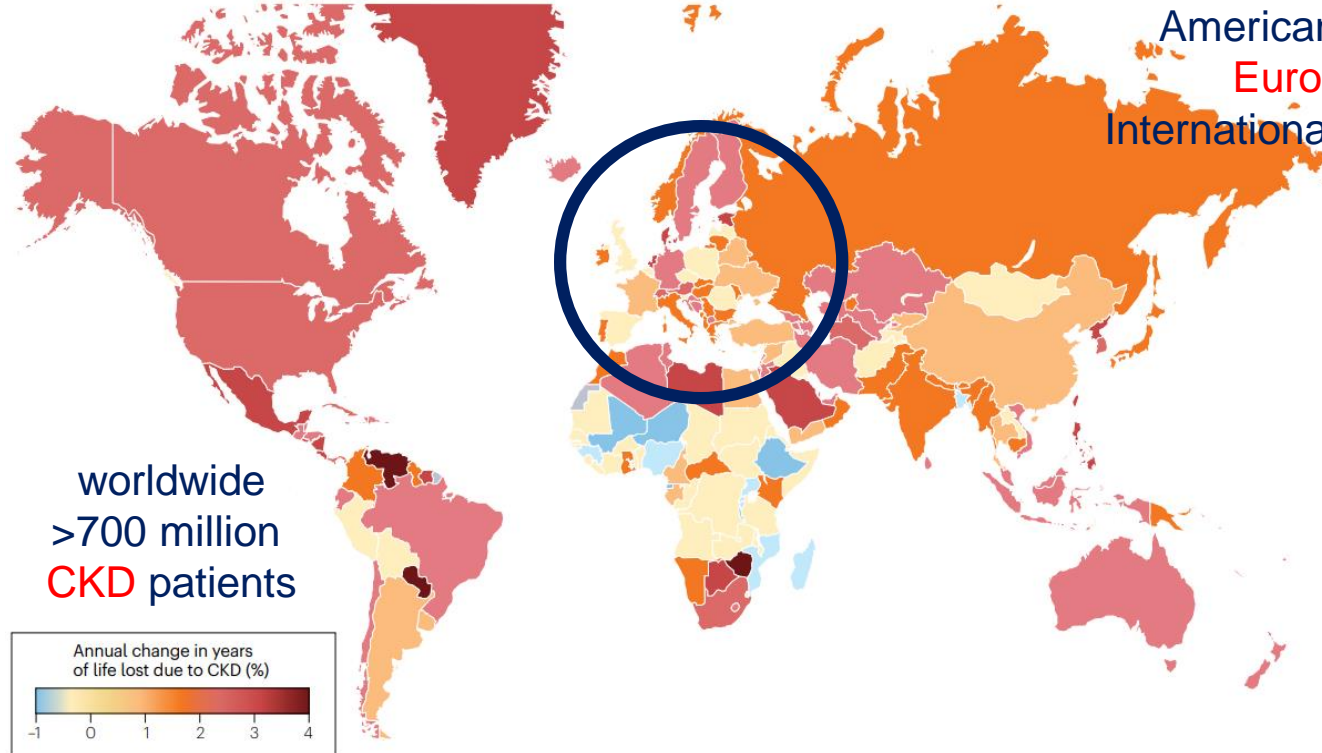
Internal Medicine IV

– Renal and Hypertensive Diseases –  
& Kidney Transplant Centre

Renal Science Chair

European Renal Association

American Society of Nephrology  
 European Renal Association  
 International Society of Nephrology



nature reviews nephrology

Consensus statement

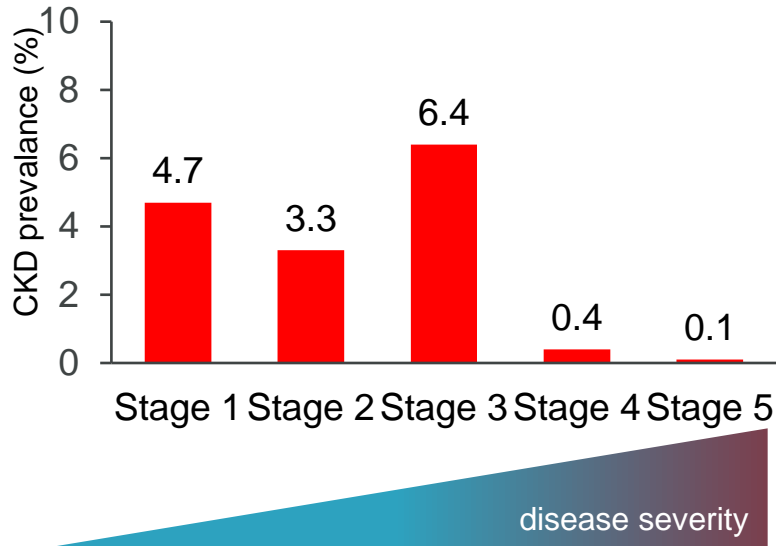
### Chronic kidney disease and the global public health agenda: an international consensus

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 Danilo Fliser<sup>7</sup>, Prabir Roy-Choudhury<sup>8</sup>, Monica Fortens<sup>9</sup>, Masenat Nengaku<sup>10</sup>, Christoph Wanner<sup>11</sup>, Cham Malla<sup>12</sup>,  
 Anne Heide<sup>13</sup>, Devendra Adh<sup>14</sup>, Susha Bawarandani<sup>15</sup>, Ana Cusumano<sup>16</sup>, Laura Sola<sup>17</sup>, Weonil Eon<sup>18</sup>,  
 Vivekanand Jay<sup>19</sup>, American Society of Nephrology<sup>20</sup>, European Renal Association<sup>21</sup> & International Society  
 of Nephrology<sup>22</sup>

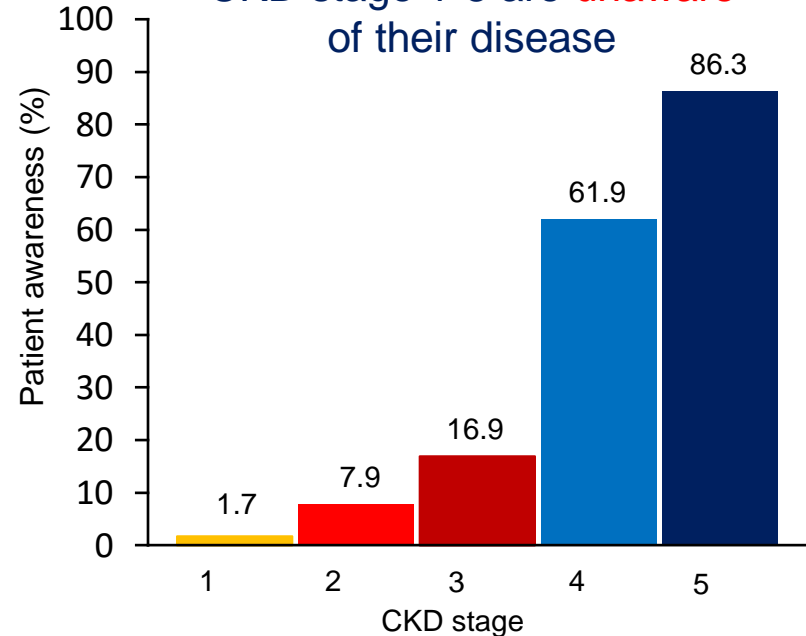
### The burden of kidney disease

- Premature mortality
- Disability
- Reduced quality of life
- Psychosocial harm
- High costs to governments and health care systems
- High costs to individuals and families, in part because of lost productivity

CKD prevalence is highest  
at CKD stage 1-3



The majority of patients with  
CKD stage 1-3 are **unaware**  
of their disease

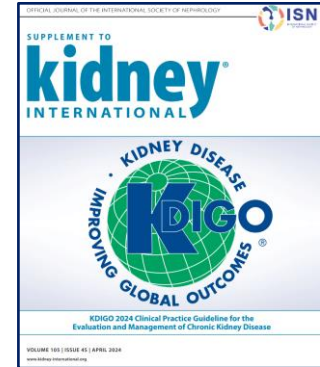


Cause  
eGFR  
Albuminuria

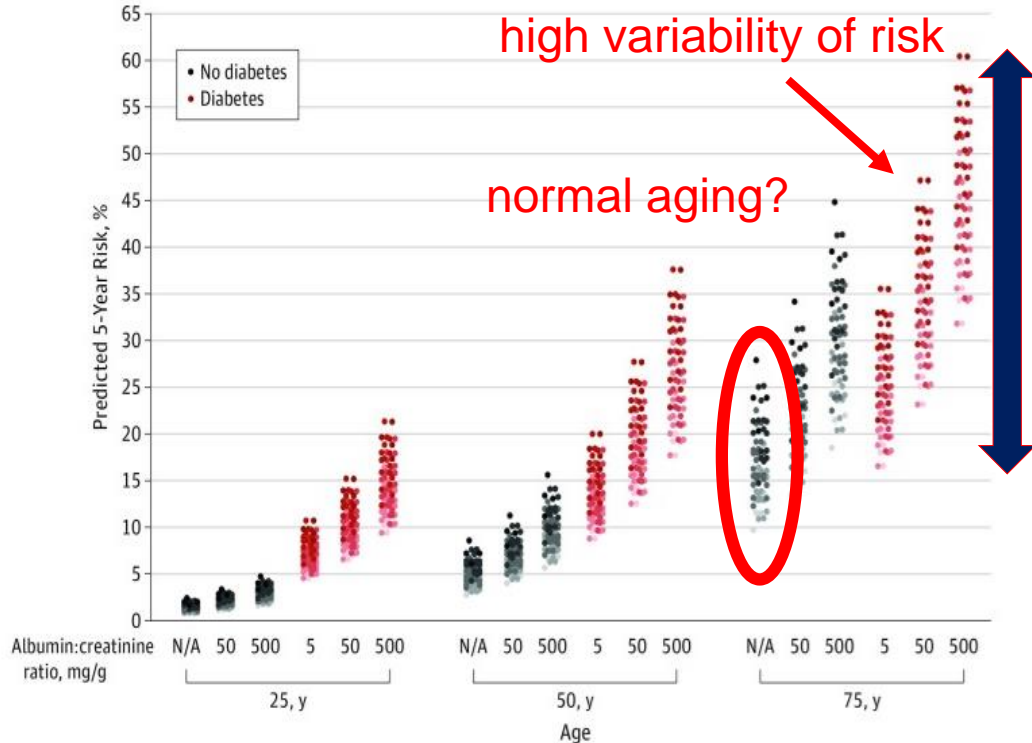
Albuminuria categories Description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol

GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

■ Low risk (if no other markers of kidney disease, no CKD)
 ■ High risk  
■ Moderately increased risk
 ■ Very high risk



# CKD progression risk



5.222.711 subjects (34 cohorts)

calculated risk of incident CKD,  
i.e. eGFR <60 ml/min/1,73m<sup>2</sup>  
(G2 → G3) in 5 years

data validated in  
2.253.540 subjects (9 cohorts)

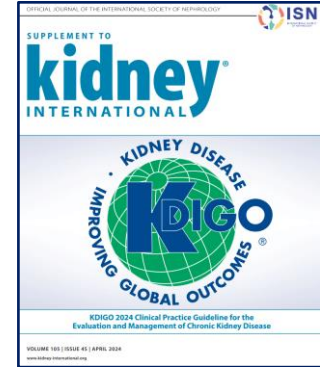


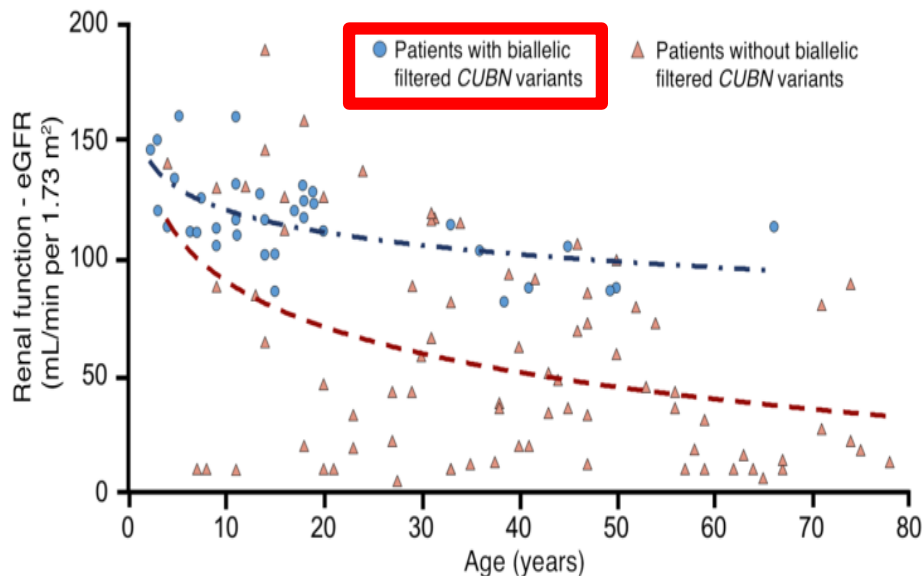
Cause  
eGFR  
Albuminuria

GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	Description and range	
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Treat* 3	Treat* 3	Treat 4+
Treat 4+	Treat 4+	Treat 4+

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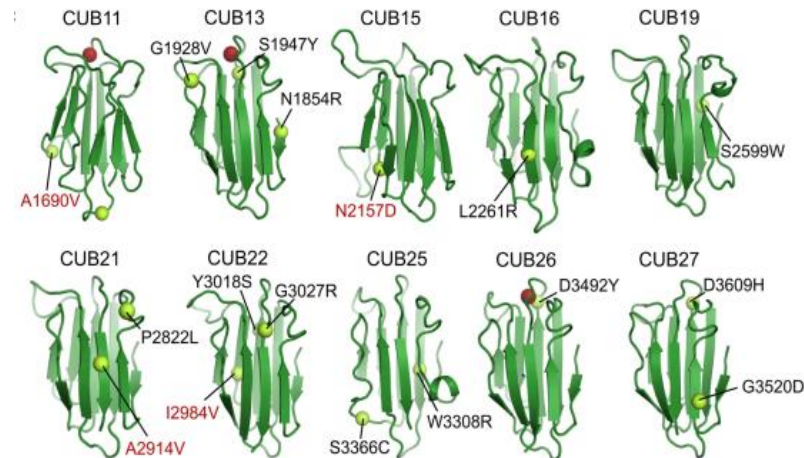


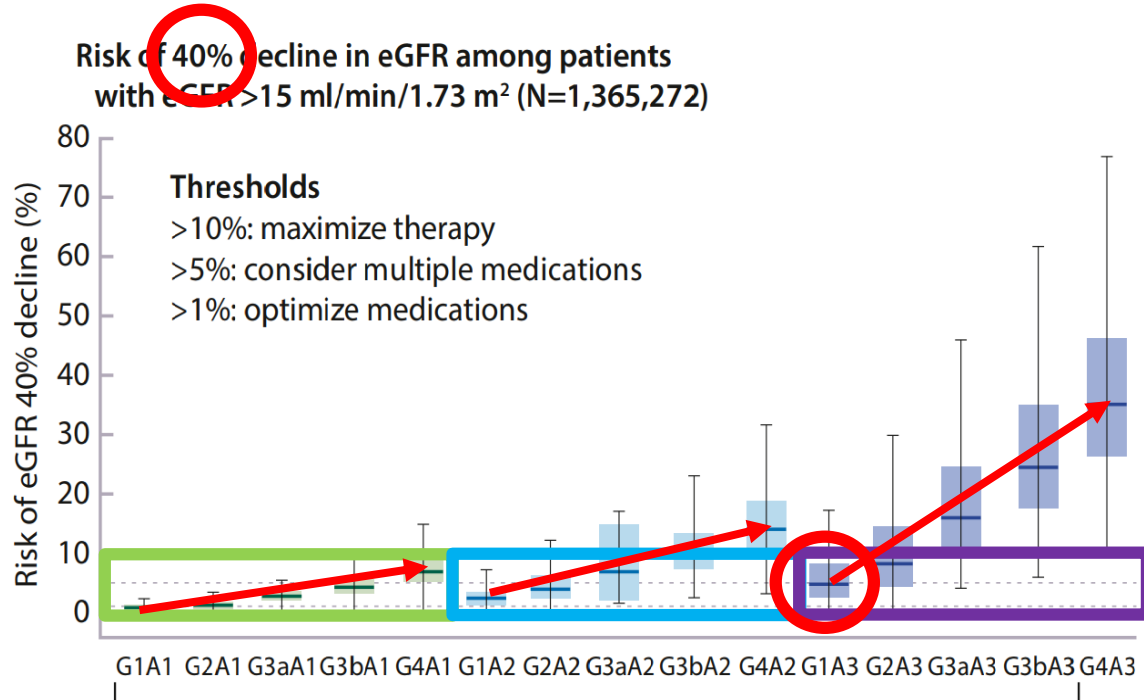
**CONCLUSION.** Collectively, our data suggest an important role for the C-terminal half of cubilin in renal albumin reabsorption. Albuminuria due to reduced cubilin function could be an unexpectedly common benign condition in humans that may not require any proteinuria-lowering treatment or renal biopsy.

The Journal of Clinical Investigation CLINICAL MEDICINE

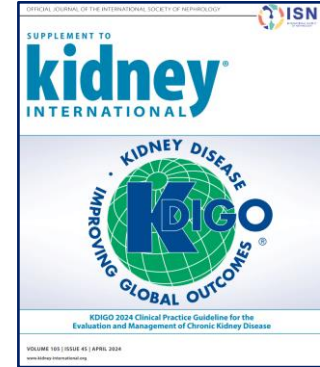
**Human C-terminal *CUBN* variants associate with chronic proteinuria and normal renal function**

Mathilda Bedin,<sup>1</sup> Olivia Boyer,<sup>2,3</sup> Aude Servais,<sup>1,4</sup> Yong Li,<sup>1</sup> Laure Villoing-Gaudé,<sup>1</sup> Marie-Joseph Tête,<sup>2</sup> Alexandra Cambies,<sup>1</sup> Julien Hogan,<sup>1</sup> Veronique Baudouin,<sup>1</sup> Saoussen Krid,<sup>1</sup> Albert Bensman,<sup>1</sup> Florie Lammens,<sup>1</sup> Ferielle Louillet,<sup>1</sup> Bruno Ranchin,<sup>1</sup> Cecile Vigneau,<sup>1</sup> Iseline Bouteau,<sup>1</sup> Corinne Isnard-Bagnis,<sup>1</sup> Christoph J. Macha,<sup>1</sup> Tobias Schäfer,<sup>1</sup> Lars Pape,<sup>1</sup> Markus Gödel,<sup>1</sup> Tobias B. Huber,<sup>1</sup> Marcus Benz,<sup>1,2</sup> Günter Klaus,<sup>1</sup> Matthias Hansen,<sup>1</sup> Kay Latta,<sup>1</sup> Olivier Cribouval,<sup>1</sup> Vincent Morinère,<sup>1</sup> Carole Tournant,<sup>1</sup> Maik Grohmann,<sup>1,2</sup> Elisa Kuhn,<sup>1</sup> Timo Wagner,<sup>1</sup> Christine Bole-Feyssot,<sup>1,2,3</sup> Fabienne Jabot-Hanin,<sup>1,2,3</sup> Patrick Nitschke,<sup>1,2,3</sup> Tarunveer S. Ahluwalia,<sup>1</sup> Anna Köttgen,<sup>1</sup> Christian Brix Folsted Andersen,<sup>1</sup> Carsten Bergmann,<sup>1,2,3</sup> Corinne Antignac,<sup>1,2</sup> and Matias Simons<sup>1</sup>





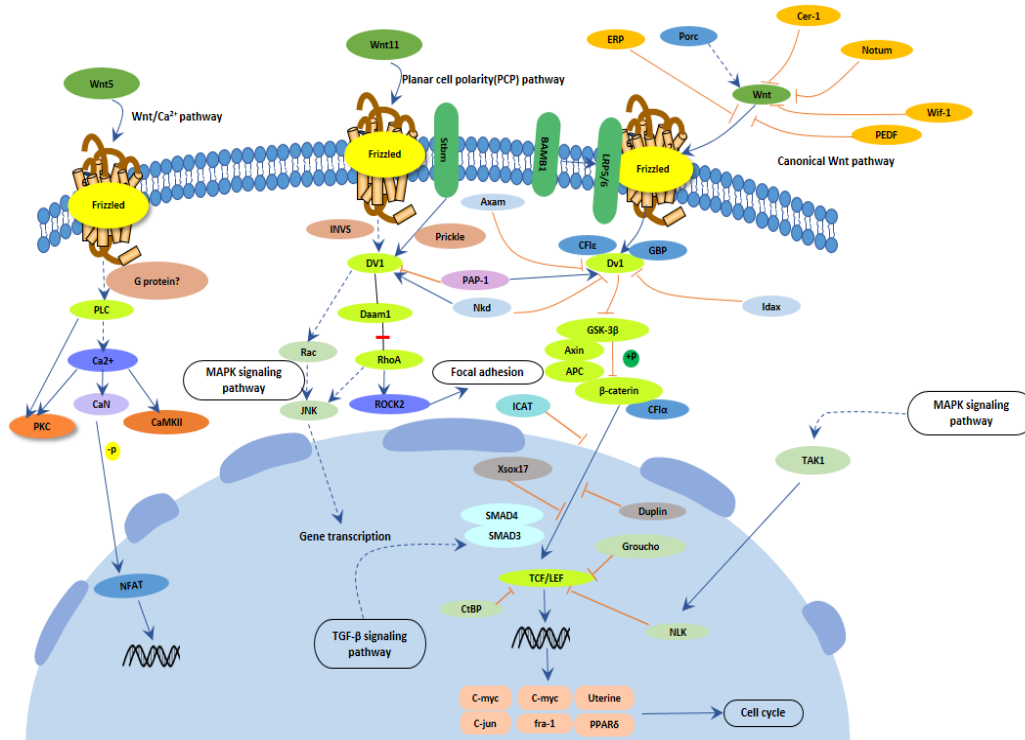
Nearly all CKD categories substantially overlap multiple risk ranges



- male, 53 years, non-smoker, no diabetes (HbA<sub>1c</sub> 5.3%)
- nephrotic syndrome since 2007!
- proteinuria 8,952 mg/24h; albuminuria 7,583 mg/24h
- s-creatinine: 0.86 mg/dl; eGFR: 99 ml/min/1,73m<sup>2</sup>
- s-cystatin C: 0.79 mg/l; eGFR creatinine-cystatin C: 108 ml/min/1,73m<sup>2</sup>
- hypertension: 150/88 mmHg despite antihypertensive combination therapy incl. losartan 100 mg/d

- kidney biopsy 2014 in USA without definite pathological finding:
  - 3/35 glomeruli sclerosed
  - moderate arteriosclerosis (hypertensive damage?)
- uDKK3: <200 pg/mg

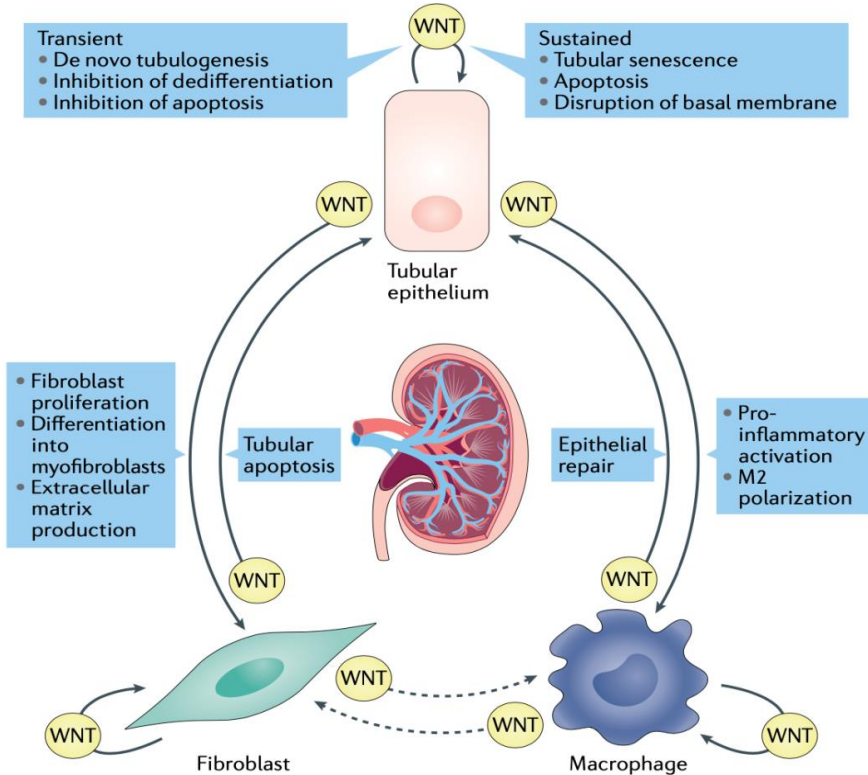
# Wnt/ $\beta$ -catenin pathway



The name Wnt is created from the names **Wingless** and **Int-1**

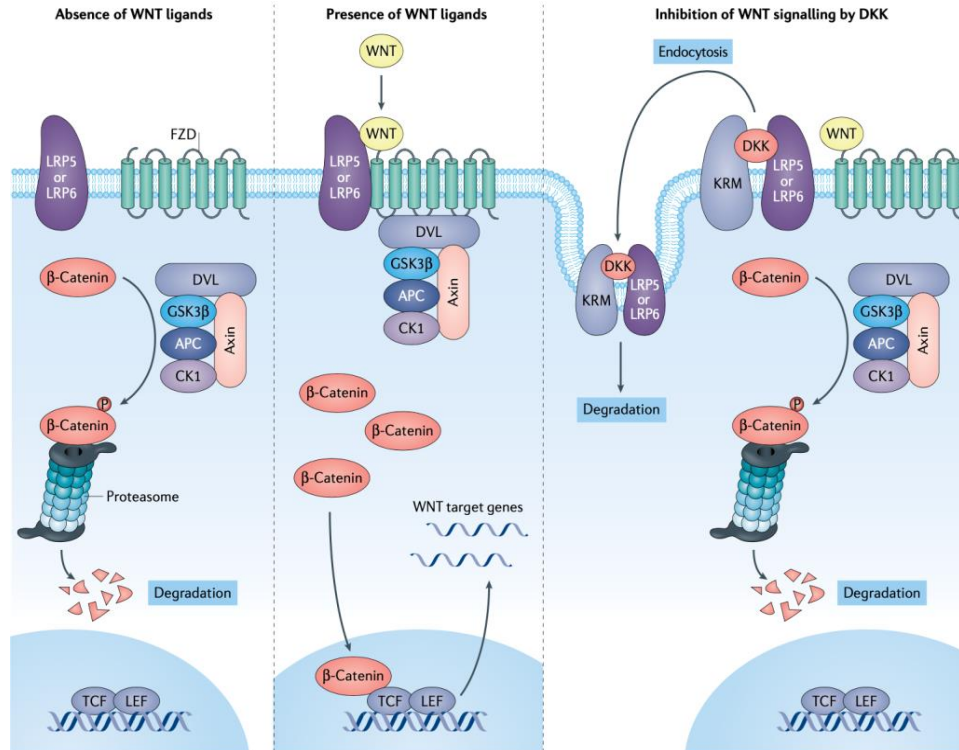
The pathway is evolutionarily highly conserved – it is similar across animal species from **fruit flies** to **humans**

# Wnt/ $\beta$ -catenin pathway



In renal tubular cells **transient** Wnt/ $\beta$ -catenin activation exerts **repair** and **regeneration** after injury

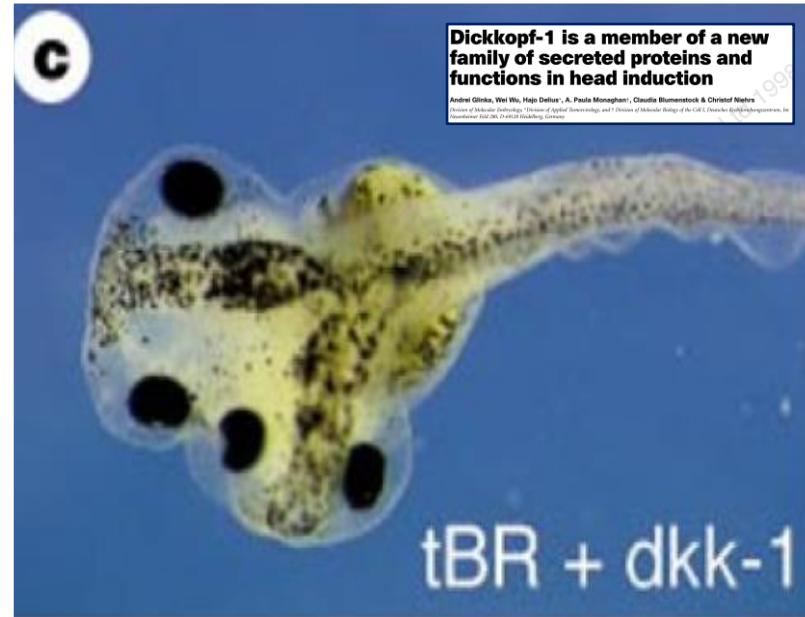
Prolonged **uncontrolled** Wnt/ $\beta$ -catenin signaling changes the phenotype of tubular cells into pro-inflammatory cells, which drive CKD **progression**, also through activation of the **RAAS**



Dickkopf (DKK) proteins serve as **modulators** (ligands) of the Wnt/ $\beta$ -catenin signaling pathway during **embryogenesis** and thereafter by re-expression after tissue injury

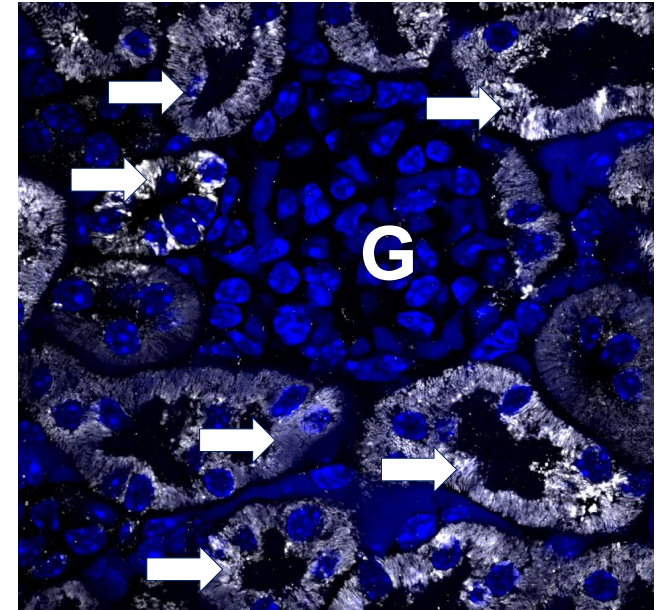
4 DKK proteins exist; mainly the role of DKK1 and DKK2 has been investigated in cancer biology

Dickkopf (German) = **big head** during enbriogenesis after knock-out of **DKK1**



DKK3 can be measured in urine using **ELISA**

Healthy subjects do not have detectable DKK3 in urine, whereas in CKD patients the urine DKK3 (**uDKK3**) concentration correlates with CKD progression irrespective of the type of kidney injury



**DKK3**  
(white staining within tubuli)

# uDKK3 and CKD progression

**JCI insight** RESEARCH ARTICLE

## Renal Dickkopf-3 promotes the development of renal atrophy and fibrosis

Georgina Federica, Michael Meisters, Daniel Mathew, Connor H. Heine, Gerhard Mühlbauer, Zoran V. Popovic, Yulia Mandelstam, Annette Kopp-Schremdes, Thomas Helberich, Peter H. Wilson, Franz Schaefer, Stefan Pischke, Danilo Florin, Bernd Assel, and Hermann Josef Gröber

Department of Cellular and Molecular Pathology and Department of Molecular Immunology, German Cancer Research Center Heidelberg, Germany; Department of Internal Medicine III, Nephrology and Hypertension, Saarland University Medical Center, Saarbrücken, Germany; Department of Biostatistics, German Cancer Research Center Heidelberg, Germany; Clinical Biochemistry Group, Department of Internal Medicine and Pediatrics II, Ludwig Maximilians University (LMU), Munich, Germany; Division of Pediatric Nephrology, University of Heidelberg, Heidelberg, Germany

Renal atrophy and interstitial fibrosis are common hallmarks of etiologically different progressive chronic kidney diseases (CKD) that eventually result in organ failure. Even though these pathological modifications constitute a major public health problem, diagnostic tools, as well as therapeutic options, are currently limited. Members of the dickkopf (DKK) family, DKK1 and DKK3, have been associated with inhibition of Wnt signaling and organ fibrosis. Here, we identify DKK3 as a stress-induced, tubular epithelial-derived, secreted glycoprotein that modulates kidney fibrosis. Genetic as well as antibody-mediated depletion of DKK3 led to reduced tubular atrophy and increased interstitial matrix accumulation in mouse models of renal fibrosis. This was facilitated by an amplified, anti-inflammatory T cell response and diminished canonical Wnt5 signaling in stressed tubular epithelial cells. Moreover, in humans, urinary DKK3 levels specifically correlated with the extent of tubular atrophy and interstitial fibrosis in different etiologies of dialysis-dependent disease. In summary, our data suggest that DKK3 constitutes an immunosuppressive and a pro-fibrotic epithelial protein that might serve as a potential therapeutic target and diagnostic marker in renal fibrosis.

J Clin Invest. 2016;126(12):3722-3732.

JCI insight 2016

**CLINICAL EPIDEMIOLOGY** www.jasn.org

## Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss

Stephan Zawinger,<sup>1</sup> Thomas Rauen,<sup>2</sup> Michael Rudnicki,<sup>3</sup> Giuseppina Federico,<sup>4</sup> Martina Wagner,<sup>5</sup> Sarah Triem,<sup>6</sup> Stefan J. Schunk,<sup>7</sup> Ismairis Petrakis,<sup>8</sup> David Schmel,<sup>9</sup> Stefan Wagner,<sup>10</sup> Hermann-Josef Gröber,<sup>11</sup> and Michael Hees,<sup>12</sup> for the German Chronic Kidney Study Group

**Abstract** Background: The identification of patients at short-term risk of eGFR loss is essential for the development of personalized medicine. We evaluated the association of urinary DKK3 with short-term risk of eGFR loss in patients with CKD. Methods: In the German Chronic Kidney Study, we measured urinary DKK3 in 1,000 patients with CKD. Results: Urinary DKK3 was associated with short-term risk of eGFR loss in patients with CKD. Conclusion: Urinary DKK3 identifies patients with short-term risk of eGFR loss.

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JASN 2018

NDT 2019

Kidney Int 2021

NDT 2021

Front Med 2022

J Clin Med 2022

Lancet Child & Adolesc Health 2023

Clin Kidney J 2024

**Articles**

## Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study

Stephan Zawinger, Michael Rudnicki, Ismairis Petrakis, David Schmel, Stefan Wagner, Sarah Triem, Stefan J. Schunk, Ismairis Petrakis, David Schmel, Stefan Wagner, Hermann-Josef Gröber, and Michael Hees, for the German Chronic Kidney Study Group

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Lancet 2019

J Nephrol 2020

JACC 2021

JACC 2021

Ped Res 2022

**ndt**

## Dickkopf-3—a novel biomarker of the kidney injury continuum

Stephan Zawinger, Michael Rudnicki, Ismairis Petrakis, David Schmel, Stefan Wagner, Sarah Triem, Stefan J. Schunk, Ismairis Petrakis, David Schmel, Stefan Wagner, Hermann-Josef Gröber, and Michael Hees, for the German Chronic Kidney Study Group

**Abstract** Background: Dickkopf-3 (DKK3) is a novel biomarker of the kidney injury continuum. We evaluated the association between urinary DKK3 and the kidney injury continuum. Methods: In the German Chronic Kidney Study, we measured urinary DKK3 in 1,000 patients with CKD. Results: Urinary DKK3 was associated with the kidney injury continuum. Conclusion: Urinary DKK3 identifies patients with the kidney injury continuum.

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NDT 2020

Front Physiol 2020

NDT 2021

**nature reviews nephrology**

## Exciting developments in the field of acute kidney injury

Chun-Tai Huang & Kathleen C. Lu

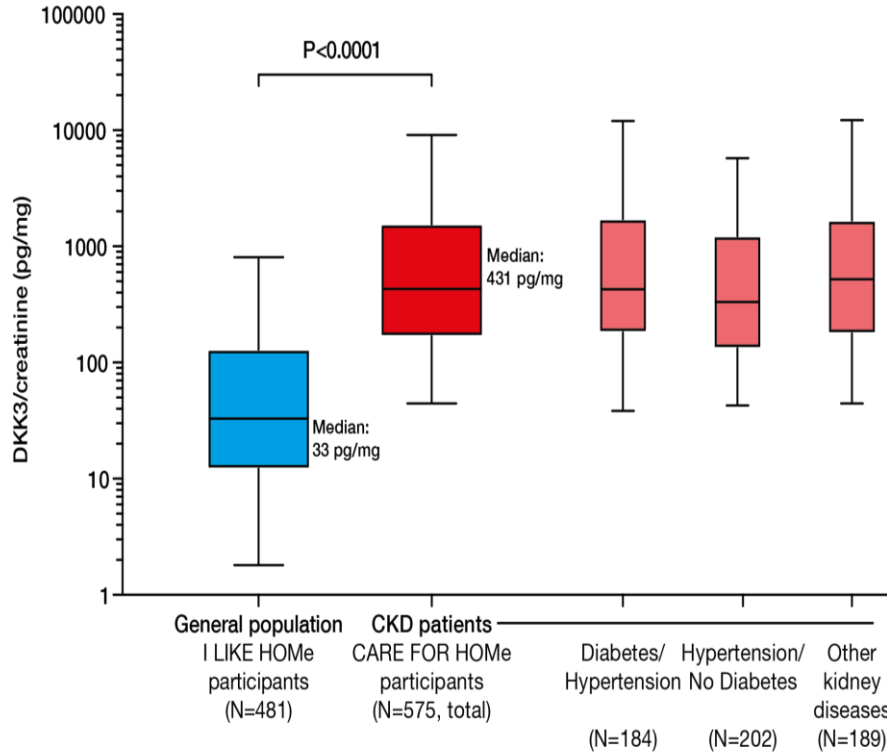
**Abstract** Acute kidney injury (AKI) is an important clinical problem that is associated with adverse short- and long-term outcomes. Studies published in 2019 provide new insights into the staging, risk stratification and subphenotyping of AKI as well as the adverse effects of AKI on the heart.

**Key advances**

- The Kidney Disease Improving Global Outcomes (KDIGO) definitions of stage 1 acute kidney injury (AKI) based on absolute versus relative changes in serum creatinine levels were associated with different outcomes in a retrospective cohort study, highlighting the potential need for revisions to current AKI definitions.
- Urinary Dickkopf-related protein 3 is a potential pre-operative biomarker for risk of AKI following elective cardiac surgery.

Nat Rev Nephrol 2020

Nat Rev Nephrol 2020



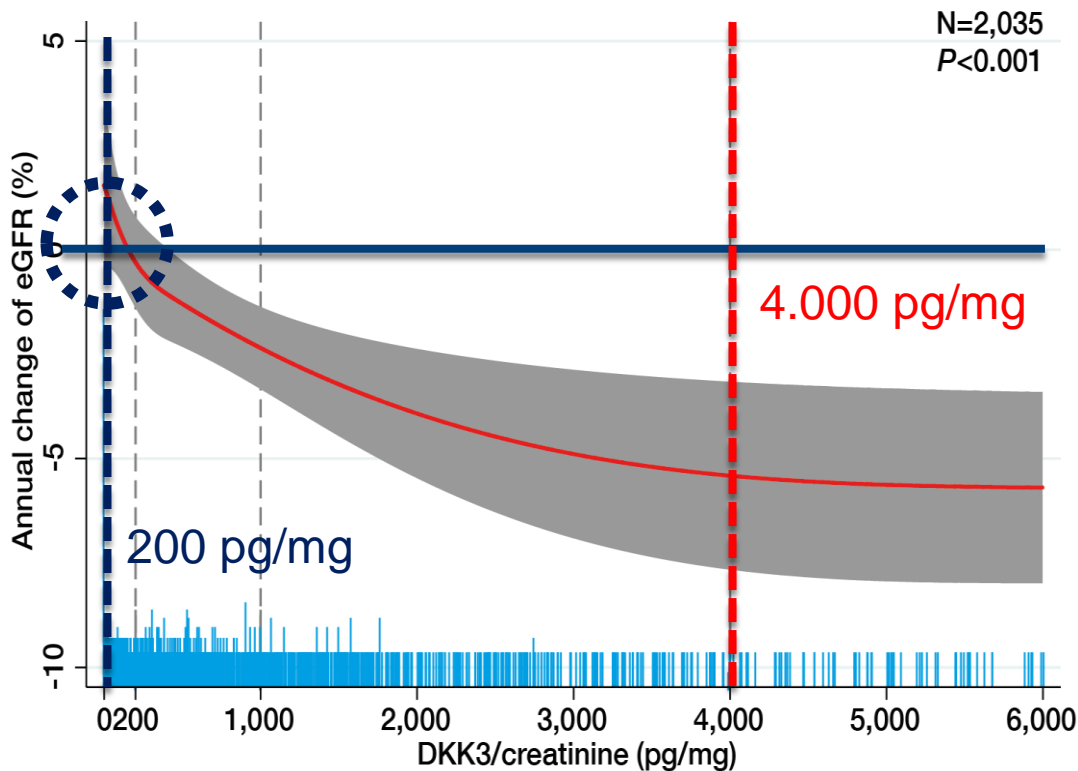
In healthy individuals only very small amounts of DKK3 are detectable in urine (blue box); in CKD patients the median urinary DKK3 level is ~13 times higher (red box) irrespective of the type of kidney injury

575 patients in CKD stage 2-4  
481 controls

## CARE FOR HOME study

- 575 patients with CKD stage 2-4 (GFR  $>15$  ml/min/1.73m<sup>2</sup>)
- mostly patients with diabetes mellitus and/or hypertension
- prospectively followed for up to 8 years ( $5.2 \pm 2.1$  years)
- annual visits with blood and urine samples
- a total of 2,035 person-years available for analysis



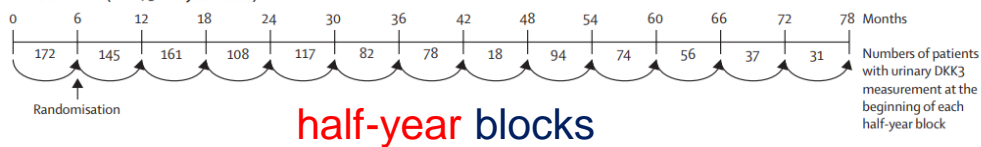


Association between uDKK3 and annual change of eGFR:

- **red line:** change of eGFR within the subsequent one year (the respective 95% confidence interval is the gray area)
- **blue spikes:** individual uDKK3 concentrations at the start of each 12-month observational period

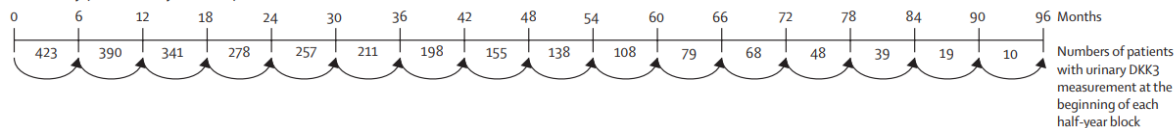


A ESCAPE trial (n=1173 half-year blocks)



ESCAPE trial

B 4C study (n=2762 half-year blocks)



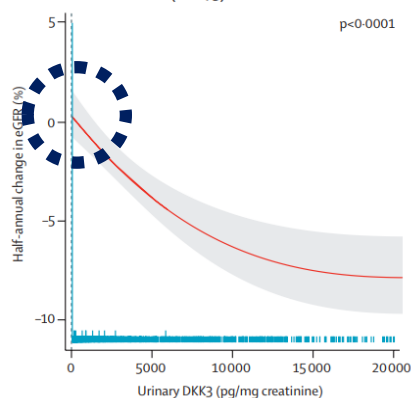
4C study

Urinary DKK3 as a biomarker for short-term kidney function decline in children with chronic kidney disease: an observational cohort study

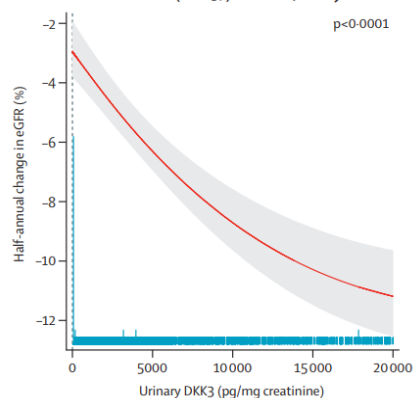
**Summary**  
Background Childhood-onset chronic kidney disease is a progressive condition that can have a major effect on life expectancy and quality. We evaluated the usefulness of the kidney tubular cell stress marker urinary Dickkopf-3 (uDKK3) in determining the short-term risk of chronic kidney disease progression in children and identifying those who will benefit from specific organoprotective interventions.

**Conclusion** uDKK3 is a useful biomarker for short-term kidney function decline in children with chronic kidney disease.

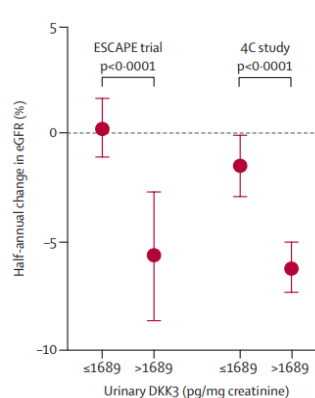
C Derivation cohort (n=1173) from the ESCAPE trial



D Validation cohort (n=2857) from the 4C study



E



uDKK3 is a **supreme biomarker** for progressive CKD:

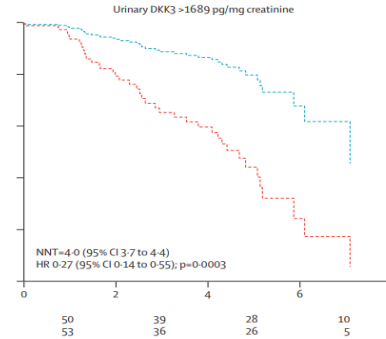
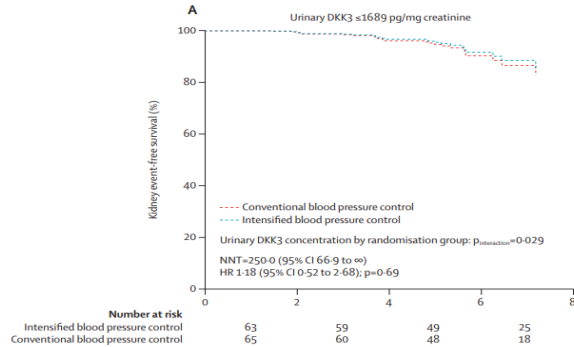
- **highly sensitive** for detection of kidney tissue injury at any time
- **non-specific**, i.e. independent of the cause of kidney injury
- **easy measurable** in children and adults
- it might be relevant for **treatment guidance** or even a potential **therapeutic target?**



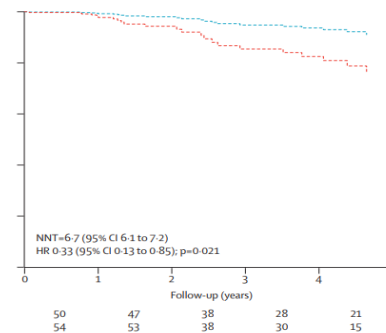
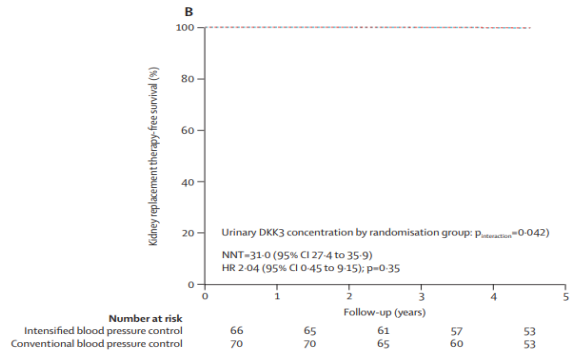
ESCAPE	all patients N=231	uDKK3 ≤1,689 pg/mg N=128	uDKK3 >1,689 pg/mg N=103	P
age (years)	12.0 ± 3.9	12.1 ± 3.8	11.7 ± 3.9	0.376
male (%)	58.9	59.9	57.7	0.792
glomerulonephritis (%)	12.9	14.6	10.6	0.159
CAKUT (%)	72.6	67.9	78.8	
others (%)	14.5	17.5	10.6	
diabetes (%)	0	0	0	0.999
hypertension (%)	3.5	3.8	3.1	0.999
systolic blood pressure	-0.01 ± 1.08	0.02 ± 1.01	-0.07 ± 1.15	0.529
eGFR (ml/min/1,73m <sup>2</sup> )	44.9 ± 20.0	54.1 ± 19.3	36.1 ± 17.0	<0.001
albuminuria (g/g)	0.66 (1.83)	0.63 (1.49)	0.73 (3.97)	0.270
uDKK3 (pg/mg)	1,098 (7,168)	160 (716)	8,693 (20,259)	<0.001

160 pg/mg

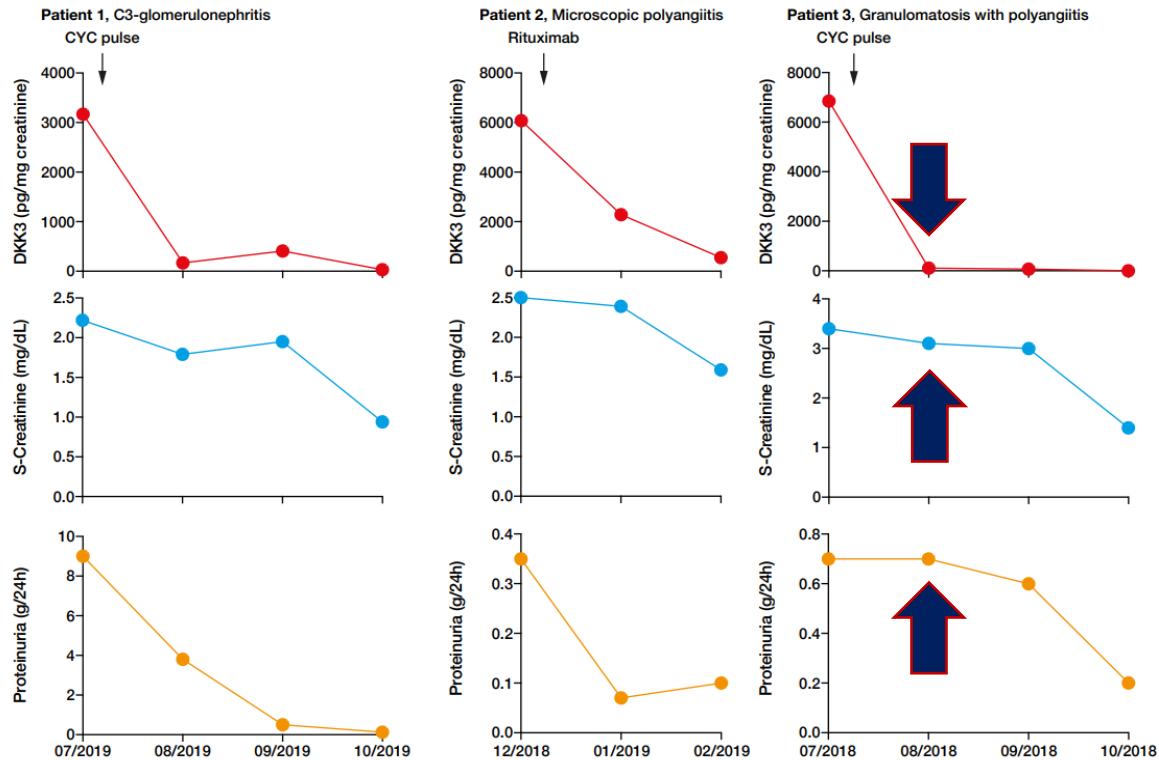
8,693 pg/mg



primary combined  
kidney endpoint  
NNT 250.0 vs. 4.0

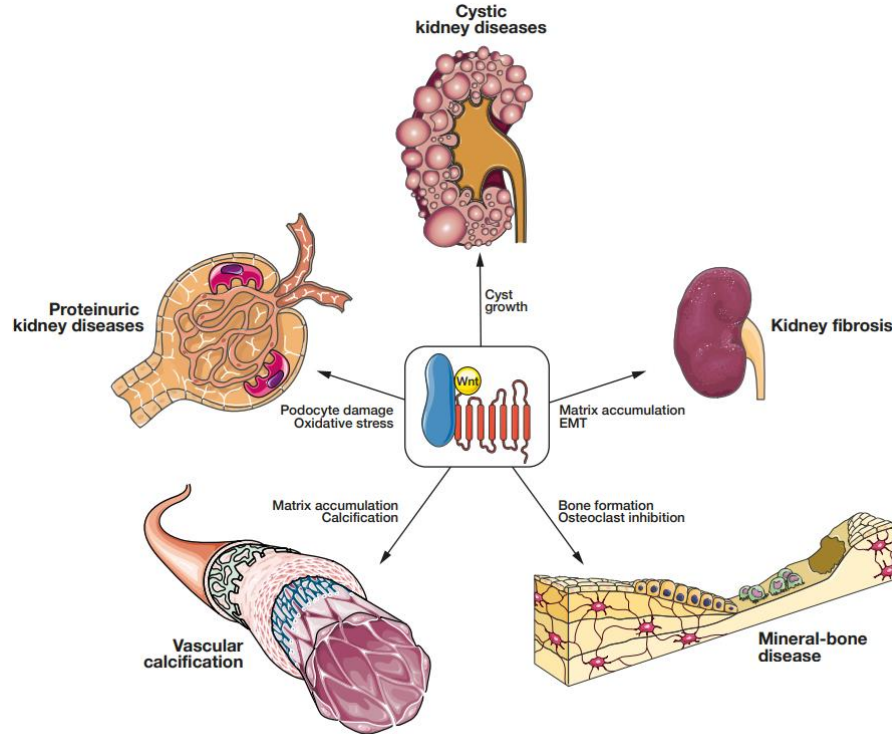


end-stage kidney  
disease (ESKD)  
NNT: 31.0 vs. 6.7



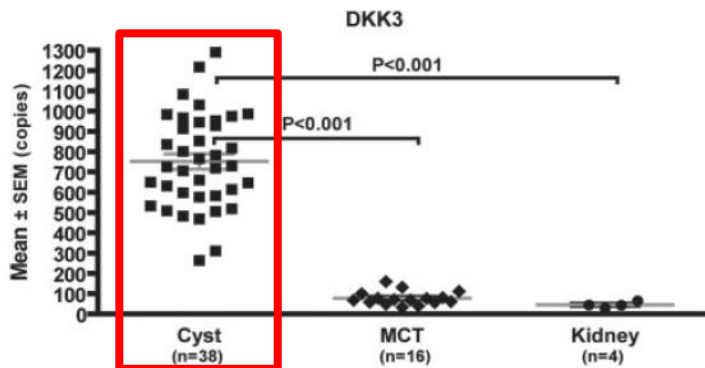
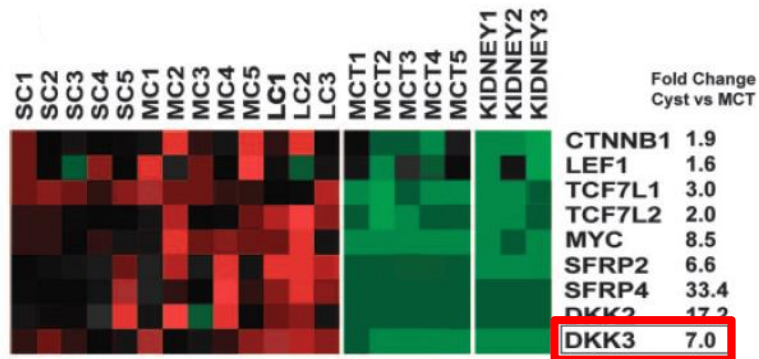


Fin del Mundo



Wnt/ $\beta$ -catenin signaling promotes:

- **cyst growth and kidney disease**
- proteinuric kidney diseases
- vascular calcification
- mineral-bone disease
- **kidney tissue fibrosis**

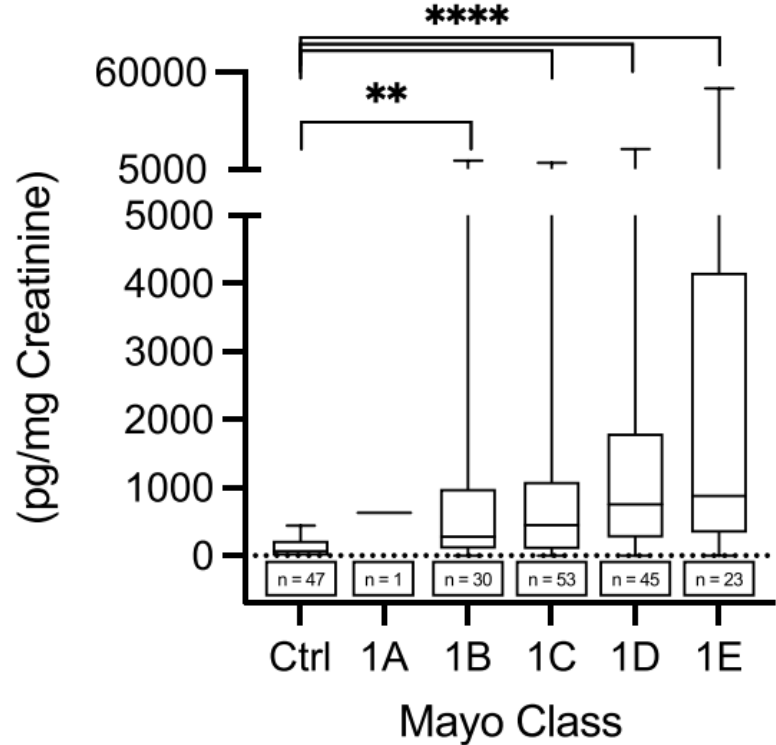
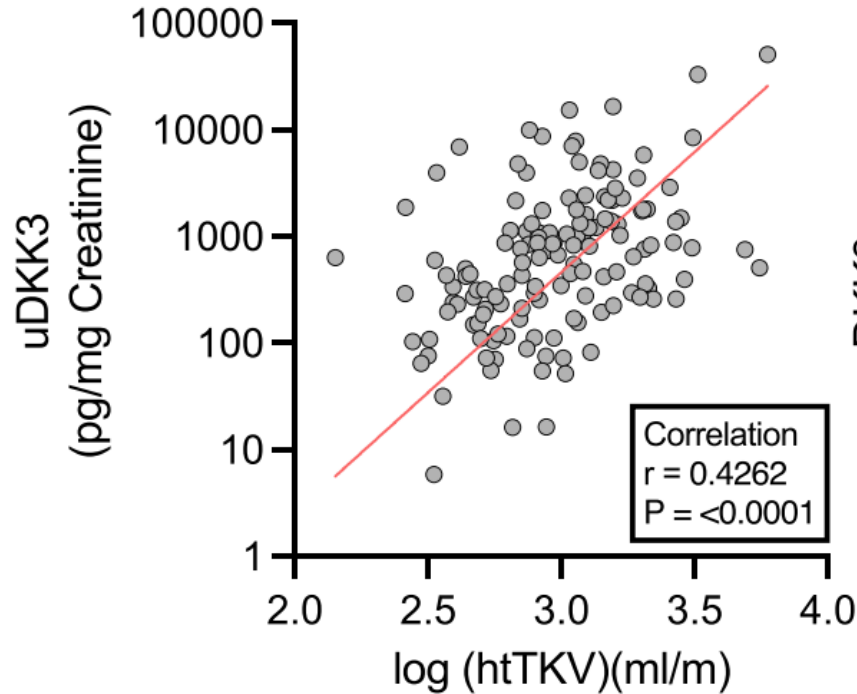


BASIC RESEARCH [www.jasn.org](http://www.jasn.org)

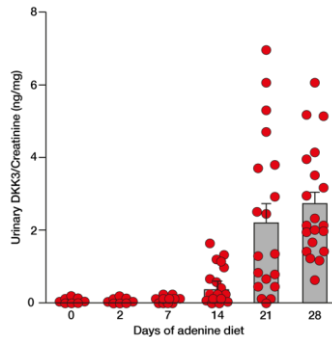
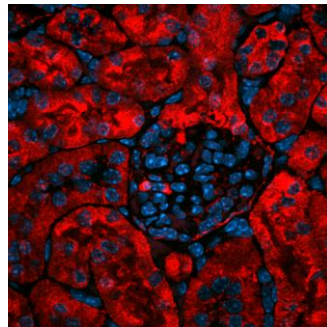
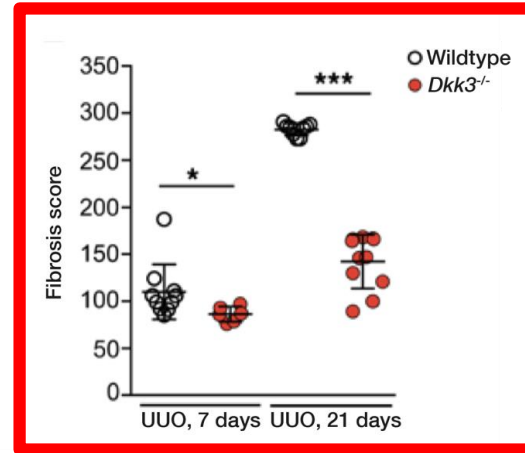
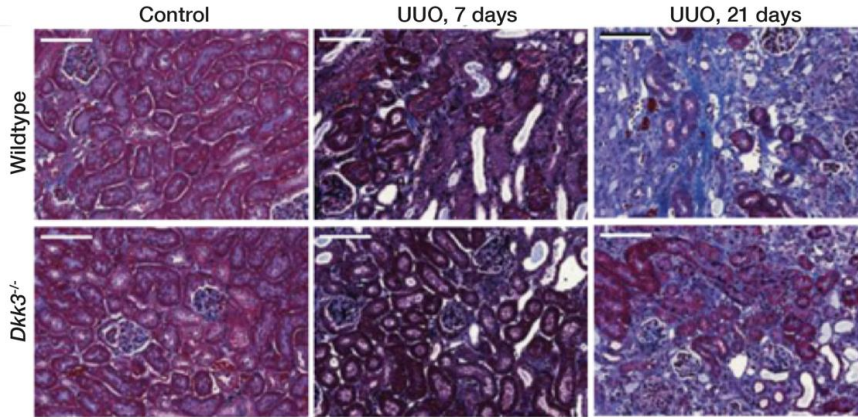
## Genetic Variation of DKK3 May Modify Renal Disease Severity in ADPKD

- high-throughput single-nucleotide polymorphism (SNP) genotyping association study of 173 candidate genes in 794 white patients from 227 families with PKD1
- real-time RT-PCR analysis of DKK3 in renal cysts

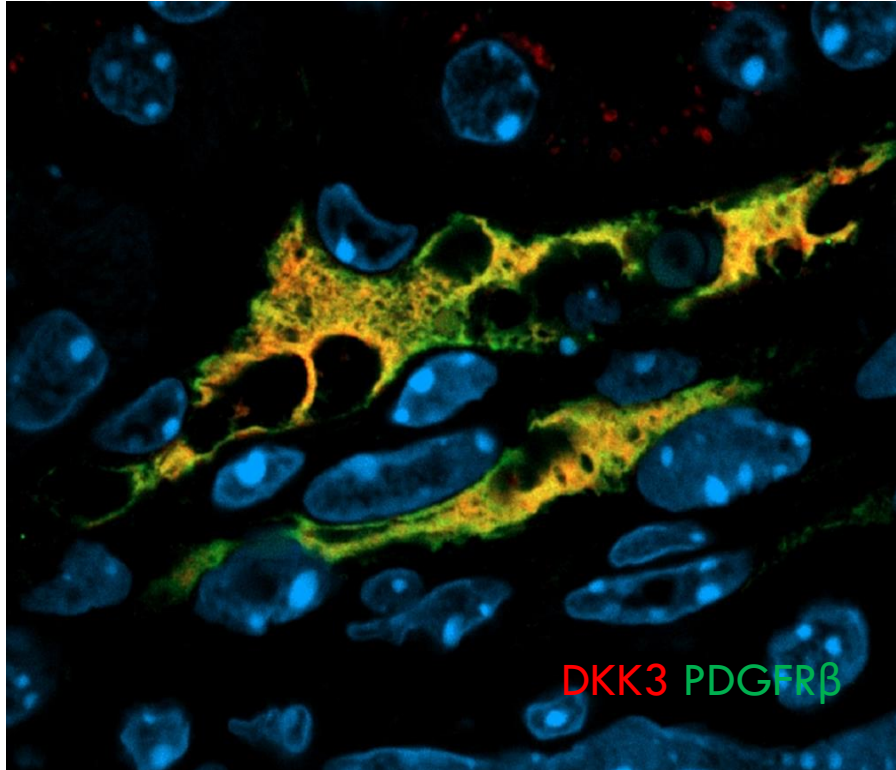
# uDKK3 and ADPKD



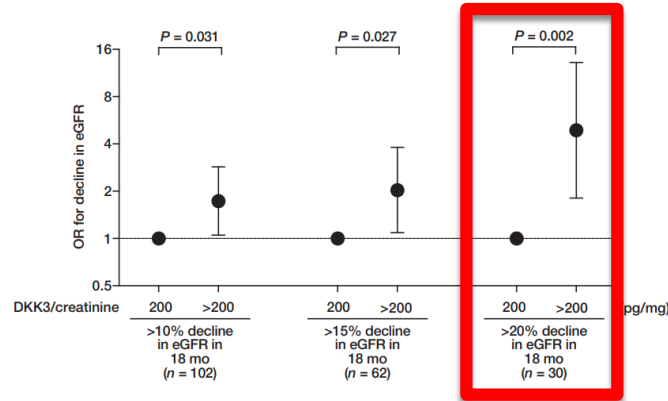
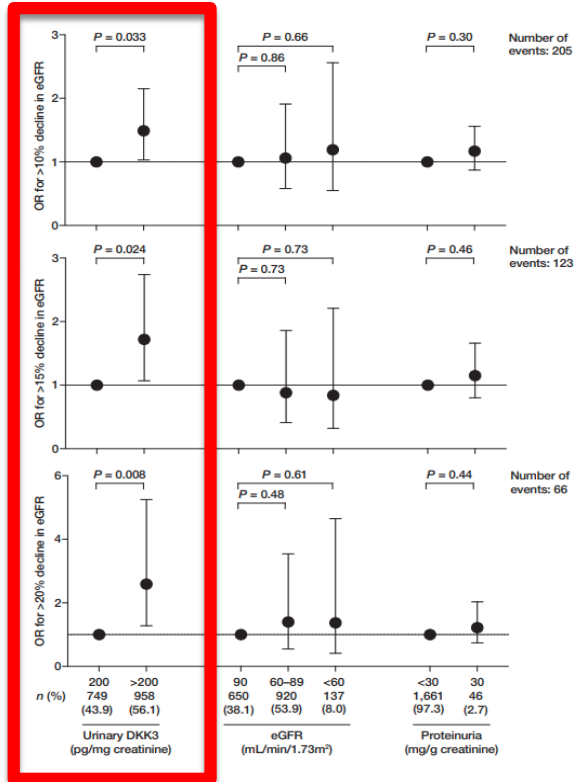
# DKK3 and kidney fibrosis



DKK3 is a **stress-induced**, mainly tubular cell derived **pro-fibrotic glycoprotein** that is secreted in the urine only upon kidney injury



- Co-staining **DKK3** and **PDGFR-β**
- fibroblasts seem to play a key role in (sustained) DKK3 expression
- they are probably „activated“ by co-localized tubular cells in a **paracrine** manner

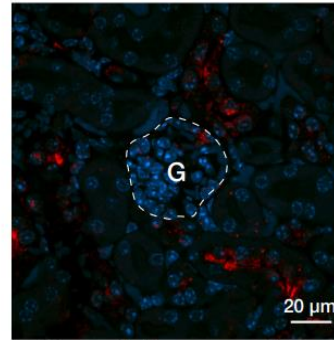
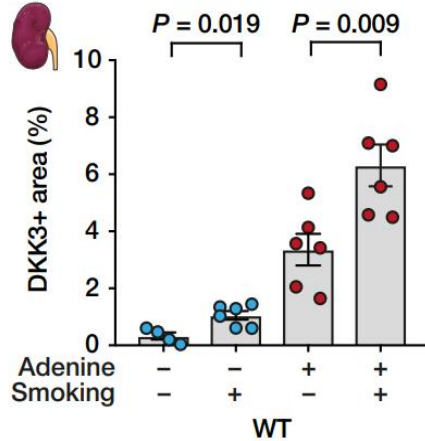


patients with  
eGFR >90 ml/min/1,73m<sup>2</sup>  
without albuminuria

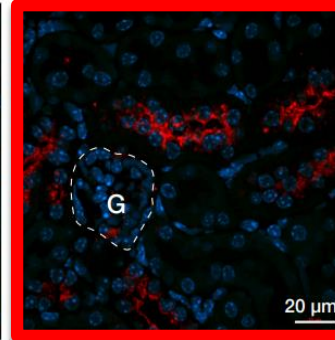
ARTICLE IN PRESS  
www.kidneyinternational.org clinical investigation  
Measurement of urinary Dickkopf-3 uncovered silent progressive kidney injury in patients with chronic obstructive pulmonary disease  
Stefan J. Schunk<sup>1</sup>, Christoph Besenwanger<sup>1</sup>, Felix Ritzmann<sup>1</sup>, Christian Herr<sup>1</sup>, Martina Wagner<sup>1</sup>, Sarah Treml<sup>1</sup>, Georg Hötter<sup>1</sup>, David Schmitz<sup>1</sup>, Stephan Zewinger<sup>1</sup>, Tamim Saadqi<sup>1</sup>, Anja Hoescher<sup>1</sup>, Peter Mahadevan<sup>1</sup>, Peter Ross<sup>1</sup>, Stefan Wiggerthel<sup>1</sup>, Rudolf Jones<sup>1</sup>, Henrik Watz<sup>1</sup>, Tobias Wehr<sup>1</sup>, Claus F. Vogelmeier<sup>1</sup>, Hermann-Josef Gröne<sup>1</sup>, Danilo Fibel<sup>1</sup>, Thimotheus Speer<sup>1,2,3</sup> and Robert Bah<sup>1,2,3</sup>

2.314 patients with  
Chronic Obstructive  
Pulmonary Disease

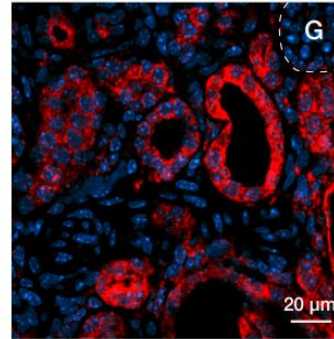
18 months follow-up



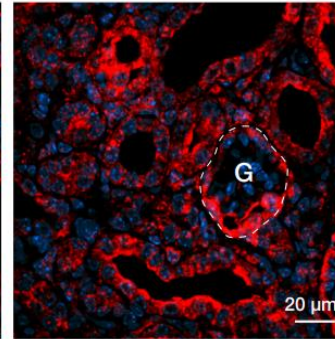
Normal diet, normal air



Normal diet, smoking

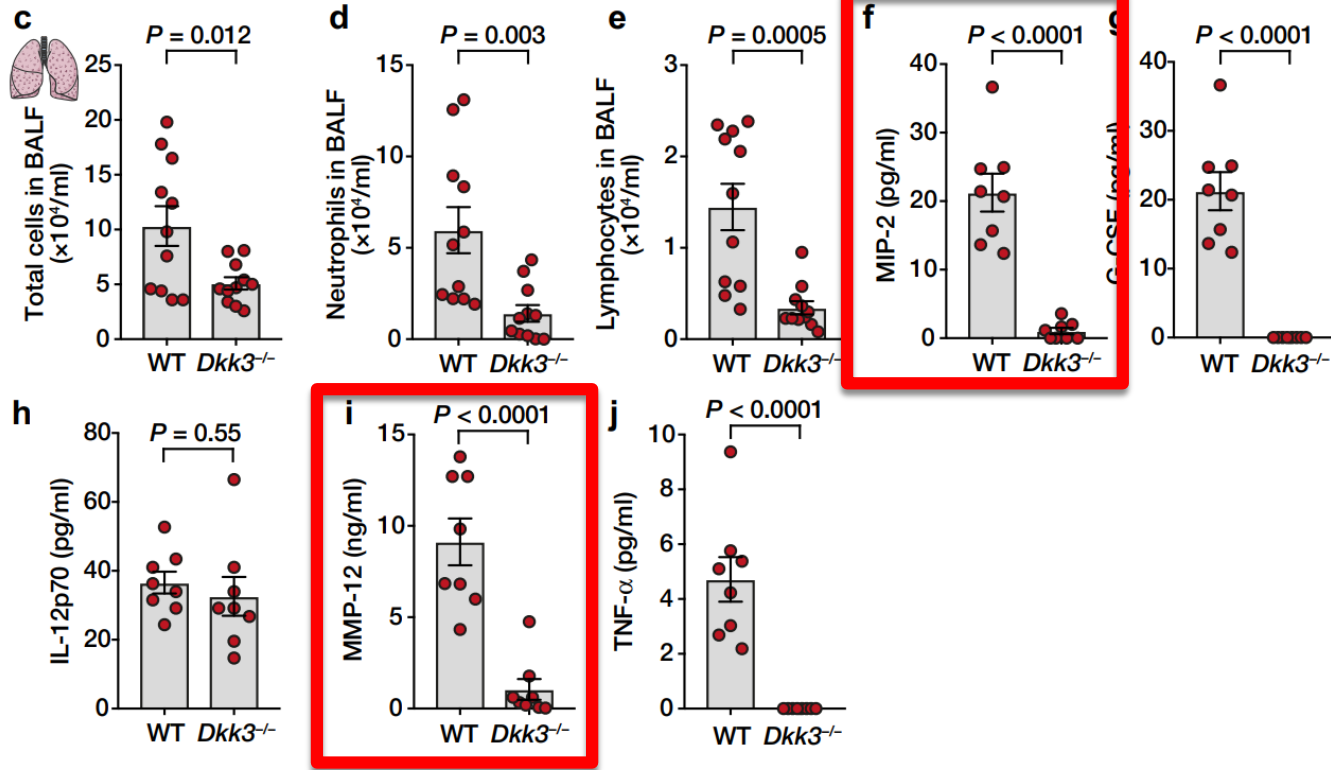


Adenine diet, normal air

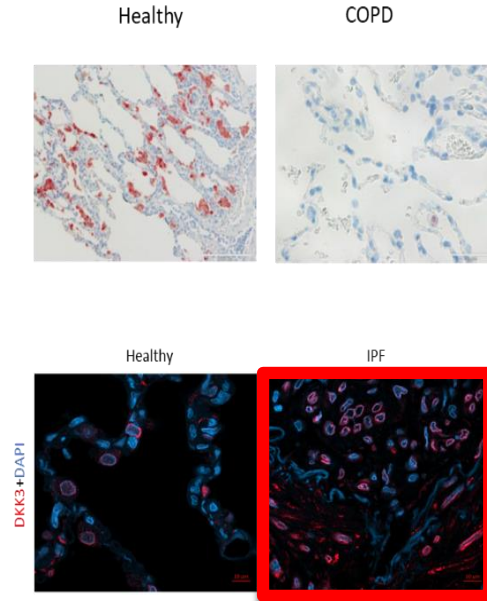
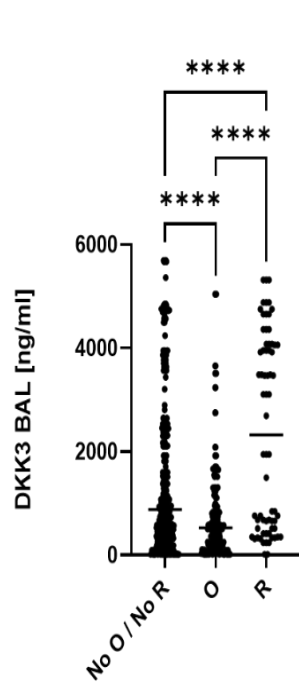


Adenine diet, smoking

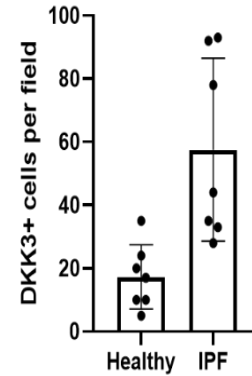
DAPI - DKK3



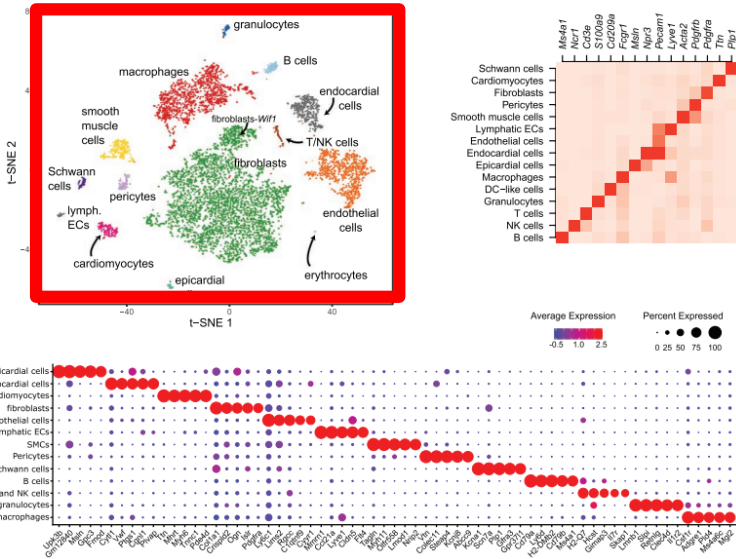
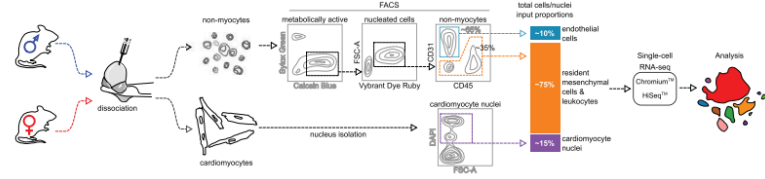
# DKK3 and the lung



DKK3 is significantly increased in the BAL fluid in patients with COPD

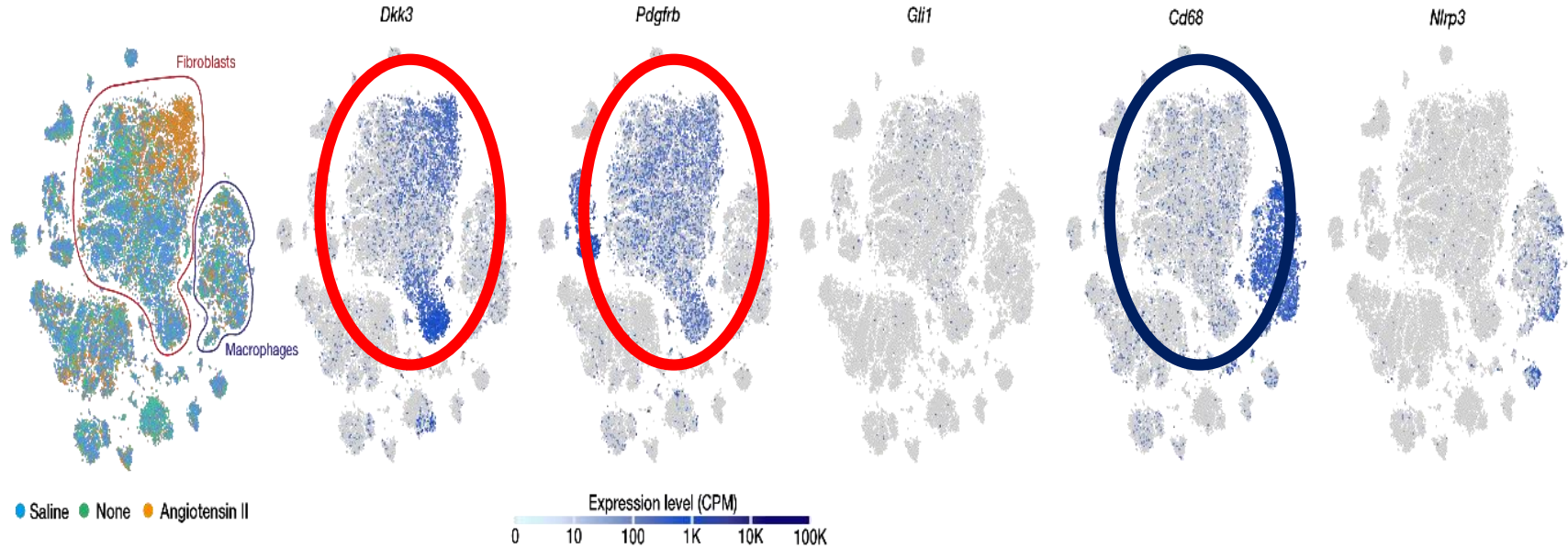


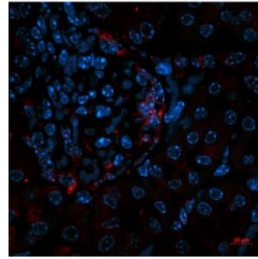
# DKK3 and the heart



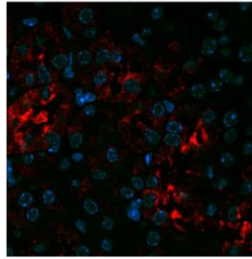
Cardiac single-cell transcriptomic strategy to characterize the cardiac cellulome – i.e. the network of cells that forms the heart – after 2 weeks of continuous administration of angiotensin II, a strong pro-fibrotic stimulus of pathological cardiac remodeling

Significant expression of **DKK3** in cardiac **fibroblasts** (PDGFR- $\beta$ +) and **macrophages** (CD68+)/NLRP3 in the left ventricle

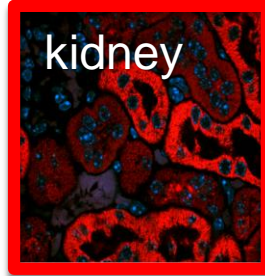




Standard diet (2 weeks)

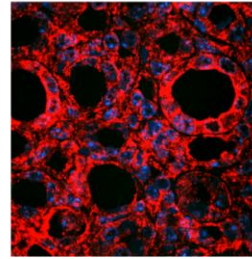


TAC operation (1 week)



kidney

TAC operation (4 weeks)

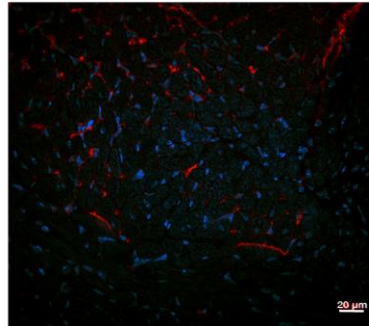


Adenine diet (2 weeks)

doi:10.1093/eurheartj/ehy083

## The new SFB/TRR219 Research Centre

A new Transregional Collaborative Research Center of the German Research Foundation (DFG) has been created to address reno-cardiovascular interactions underlying the increased cardiovascular risk in patients with chronic kidney disease to develop novel treatment strategies to reduce cardiovascular morbidity and mortality in these high-risk patients



TAC 1 week



heart

TAC 4 weeks

DKK3 DAPI

uDKK3 is a **supreme biomarker** for progressive CKD:

- **highly sensitive** for detection of kidney tissue injury at any time
- **non-specific**, i.e. independent of the cause of kidney injury
- **easy measurable** in children and adults
- it may be relevant for **treatment guidance** as well as a potential therapeutic target to **prevent tissue fibrosis**



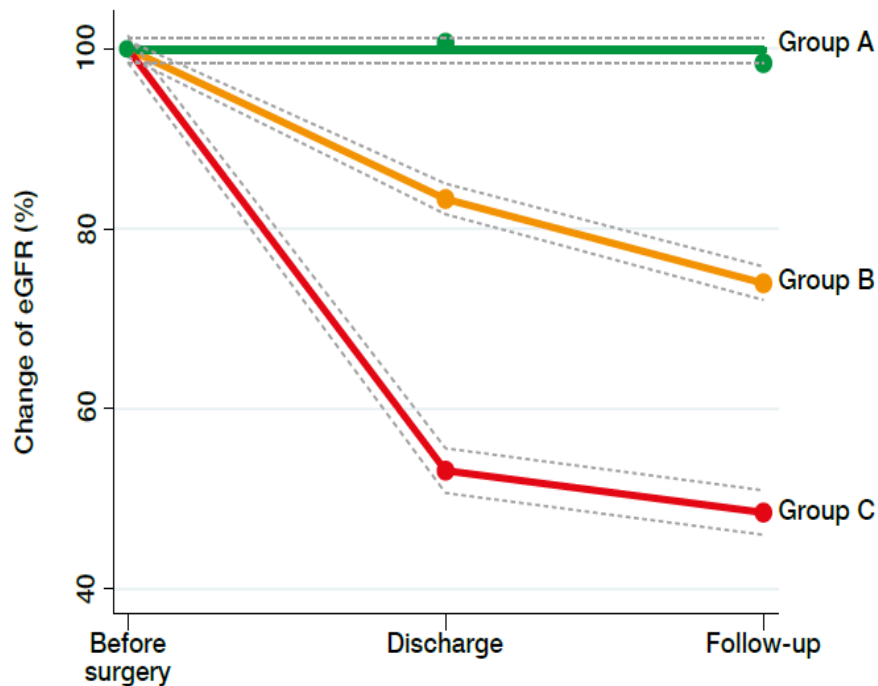
UKS  
Universitätsklinikum  
des Saarlandes

# Thank you!



## HTC study

- prospective observational study with **733** consecutive patients undergoing **elective cardiac surgery** (mean eGFR **89** ml/min/1.73m<sup>2</sup>)
- assessment of kidney function (eGFR) before surgery, after hospital discharge and up to 3 years thereafter (median follow-up **820** days)
- measurement of **uDKK3 before surgery**



3 distinct eGFR trajectories corresponding to patients with:

- **group A (low uDKK3):** no AKI and no loss of kidney function
- **group B (high uDKK3):** moderate loss of GFR after AKI and CKD progression
- **group C (very high uDKK3):** severe loss of GFR after AKI and CKD progression