Targeting tubular reabsorption for kidney protection

Fact Sheet

**Project information**

**RENOPROTECT**

 Grant agreement ID: 865408

 Status

 Grant agreement signed

 Start date 1 August 2020  

 End date 31 July 2025

 Funded under: H2020-EU.1.1.

 Overall budget:

 € 1 945 250

 EU contribution

 € 1 945 250

 Hosted by: UNIVERSITATSKLINIKUM HEIDELBERG

 Germany

**Objective**

Many forms of chronic kidney disease are featured by the loss of protein into the urine (proteinuria). When the cause of proteinuria lies within the glomerulus, such as in diabetic kidney disease, then the protein overload in the tubular lumen may lead to damage of the downstream tubular cells. Particularly vulnerable are proximal tubular cells (PTCs), because these cells are specialized in protein reabsorption and have a high metabolic demand. Dysfunction of the main albumin uptake receptor cubilin (encoded by the CUBN gene) leads to the reduction of albumin uptake and albuminuria. Here, we hypothesize that genetic variants in CUBN are key for providing a cell-to-cell variability that is beneficial for PTC homeostasis and resistance against proteinuric kidney disease. This hypothesis is based on our recent findings that 1.) CUBN mutations are well tolerated by humans despite their proteinuric effects and that 2.) the CUBN locus shows signatures of balancing selection during human evolution. To address this hypothesis, we will first functionally validate common CUBN variants and haplotypes in a humanized Drosophila model and test whether they provide protection against renal disease in mice. Second, we will explore monoallelic CUBN expression and partial cryptic exon inclusion as two possible genetic mechanisms by which CUBN variants could promote proximal tubule fitness and tissue repair. Finally, taking advantage of cubilin dysfunction as a “safe” means to avoid PTC overload, we will target PTC protein uptake in proteinuric mice with the help of a nanoparticle delivery method. Altogether, our integrative translational approach will combine human genetics and experimental studies to explore a new mechanism of proximal tubule homeostasis that may also be applicable to other tissues. Based on evolutionary genetics, we aim to establish a novel paradigm
for kidney protection with high relevance for the diagnosis, prognosis and treatment of proteinuric kidney disease.

Programme(s)

H2020-EU.1.1. - EXCELLENT SCIENCE - European Research Council (ERC)

Topic(s)

ERC-2019-COG - ERC Consolidator Grant

Call for proposal

ERC-2019-COG

See other projects for this call

Funding Scheme

ERC-COG - Consolidator Grant

Host institution

UNIVERSITATSKLINIKUM HEIDELBERG

Address
Im Neuenheimer Feld 672
69120 Heidelberg

Activity type
Higher or Secondary Education Establishments

EU Contribution
€ 1 945 250

Website
Contact the organisation

Beneficiaries (1)

UNIVERSITATSKLINIKUM HEIDELBERG

Address
Im Neuenheimer Feld 672
69120 Heidelberg

Activity type
Higher or Secondary Education Establishments

EU Contribution
€ 1 945 250

Website
Contact the organisation