Overcome obstacles in the treatment of scarred kidneys

More than 10% of the world's population suffer from chronic kidney disease (CKD), a serious disorder that leads to a prominent reduction in quality of life and might end fatally. Independent of its initial cause, virtually all kidneys of patients with CKD are characterized by kidney scarring termed renal fibrosis, i.e. replacement of functional kidney tissue by non-functional connective tissue. Today's treatment options for CKD patients are very limited. Although fibrosis is the common pathological process in CKD and therefore represents an excellent treatment target, only very few clinical trials with anti-fibrotic drugs were conducted in CKD patients. None of those trials let to a new therapy option for CKD patients yet. In our article, we summarized the very few existing clinical trials in renal fibrosis.

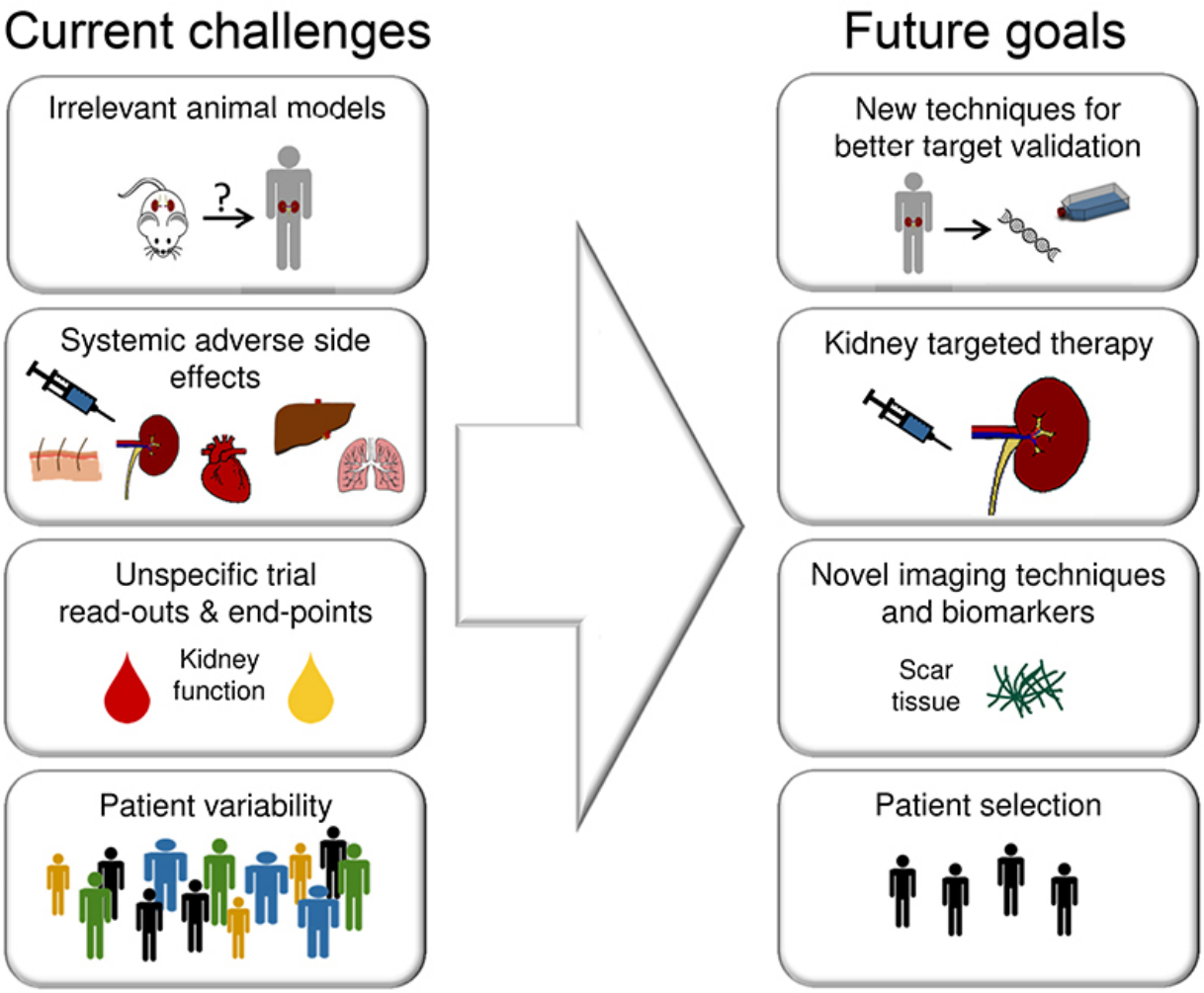

Fig. 1. Current challenges and solutions for successful anti-fibrotic trials in CKD patients. (modified from: Klinkhammer, B.M., Goldschmeding, R., Floege, J., Boor, P., 2017. Treatment of Renal Fibrosis-Turning Challenges into Opportunities. Adv Chronic Kidney Dis 24 (2), 117-129.)

We discussed some major reasons for the lack of new clinical trials, i.e. poor translation ‘from bench to bedside’, and suggested some solutions which might help to find an effective anti-fibrotic therapy for CKD patients. In particular we discussed the following issues:

Animal models are the main method in pre-clinical research. However, they do not perfectly depict the human situation. E.g. most animals used are young, kept under standardized conditions and the models induce CKD within a few weeks, while most of CKD patients are old, develop CKD over years and have other diseases and medications, different lifestyles and environmental conditions. To facilitate translation, more *relevant pre-clinical models* and better tools for *confirmation of therapeutic targets* in renal tissue should be used, e.g. within the frame of biobanks or high-throughput screening assays with human cells or tissues.

There are currently no drugs for CKD that would specifically target the kidney. Systemic use of anti-fibrotic agents might lead to adverse side effects that might limit long-term treatment. To circumvent this, focus should be on *kidney specific therapies*, e.g. by targeting effective drugs specifically to kidney cells.

Currently, renal fibrosis can only be assessed specifically by renal biopsy and the efficacy of anti-fibrotic drugs could only be validated using repeated renal biopsies, which is not feasible due to its invasive nature. Therefore, anti-fibrotic CKD trials have to use approved, but less specific and variable but parameters of kidney function as outcomes defining the efficacy of the new treatment. *Quantifiable, repeatable methods for specific analyses of fibrosis in kidneys*, e.g. biomarkers in blood or urine or advanced imaging techniques, are required.

In the current clinical trials patient populations are very heterogeneous, e.g. with regard to underlying diseases, age, lifestyle, stage of fibrosis, etc. This variability might strongly influence their responsiveness to specific anti-fibrotic treatments. A selection of more *homogenous patient groups* that would benefit most of a given therapy will be needed also for CKD patients.

Given the world-wide burden of CKD, overcoming these translational challenges and improving drug development should be one of the research priorities for the future.

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Publication

Treatment of Renal Fibrosis-Turning Challenges into Opportunities.

Klinkhammer BM, Goldschmeding R, Floege J, Boor P
Adv Chronic Kidney Dis. 2017 Mar