Characterization of the unilateral ischemia-reperfusion-injury (uIRI) mouse model of of chronic kidney disease (CKD)

Authors
Maria Ougaard, Helene Dyhr, Ditte Marie Jensen, Frederikke Emilie Sembach & Michael Christensen

Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author
Michael Christensen - MCH@gubra.dk

BACKGROUND & AIM

Ischemia-reperfusion-injury (IRI) is one of the leading causes of acute kidney injury (AKI) which poses an increased risk for development of chronic kidney disease (CKD). Renal IRI involves temporary impairment with subsequent restoration of oxygen and nutrient delivery to kidney cells, triggering inflammatory and fibrotic injury. Further insight into the pathophysiological mechanisms underlying transition from AKI to CKD is important for developing more efficacious drug treatments.
Here, we characterized the uIRI mouse model for long-term changes in plasma and histological markers of kidney injury.

METHODS

Male C57Bl/6J mice (10 weeks old) were randomised into study groups based on body weight. All mice received standard chow (Altromin 1324, Brogaarden DK). Vehicle dosing was initiated on day -2 until termination. On day 1, mice in group 1 were sham-operated and group 2 underwent uIRI surgery (35 min obstruction of blood flow of the left kidney). After 6 weeks, mice were terminated. At week 1, 3 and 6 plasma was collected for KIM-1 analysis. Terminal plasma was sampled for creatinine and urea analysis. Kidneys were sampled, weighed and the left kidney was processed for histological evaluation of inflammation (F4/80), tubular injury (KIM-1) and fibrosis (Col3a1).

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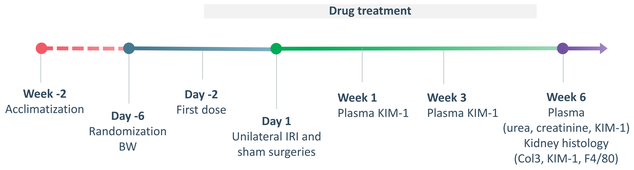
1 Study Outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume
1	Sham Vehicle	Male	10	**Vehicle**	PO	QD	5 ml/kg
2	uIRI Vehicle	Male	12	**Vehicle**	PO	QD	5 ml/kg

2 Body weight, and kidney weight

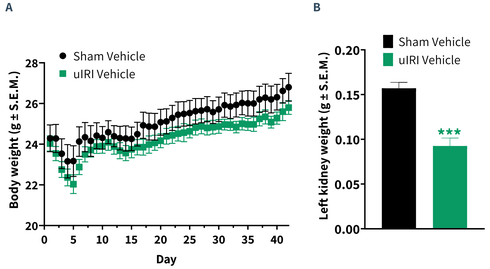


Figure 2. Body weight, kidney- and heart weight. (A) Body weight (% of day 1). **(B)** Left kidney weight at termination, week 6. Mean + SEM, n = 10-12. ***p<0.001 compared to Sham Vehicle (Dunnett's test one-factor linear model).

3 uIRI mice show increased plasma creatinine, urea and KIM-1

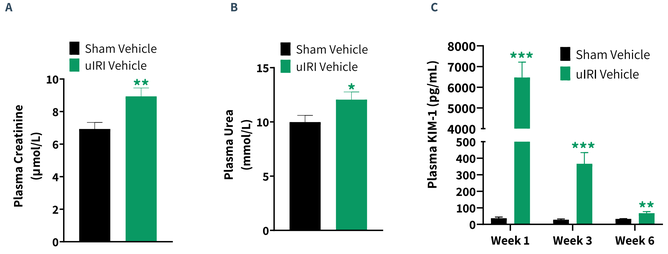


Figure 3. IRI-CKD mice show increased terminal plasma creatinine and urea levels with gradual normalization of plasma KIM-1 levels. (A) Plasma creatinine at 6 weeks. **(B)** Plasma urea at 6 weeks. **(C)** Plasma KIM-1 levels at week 1, 3 and 6. Mean + SEM, n = 10-12. *p<0.05, **p<0.01, ***p<0.001 compared to Sham Vehicle (Dunnett's test one-factor linear model).

4 uIRI mice develops kidney inflammation

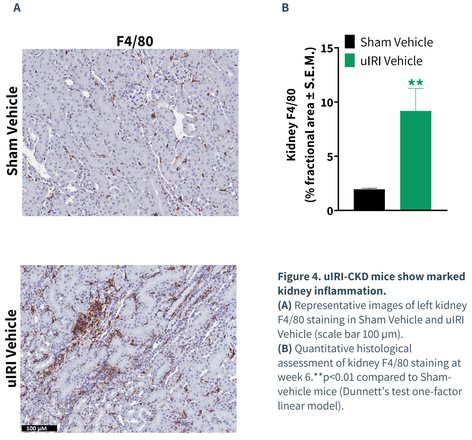


Figure 4. uIRI-CKD mice show marked kidney inflammation.
(A) Representative images of left kidney F4/80 staining in Sham Vehicle and uIRI Vehicle (scale bar 100 µm).
(B) Quantitative histological assessment of kidney F4/80 staining at week 6.**p<0.01 compared to Sham-vehicle mice (Dunnett's test one-factor linear model).

5 uIRI mice develop tubular injury

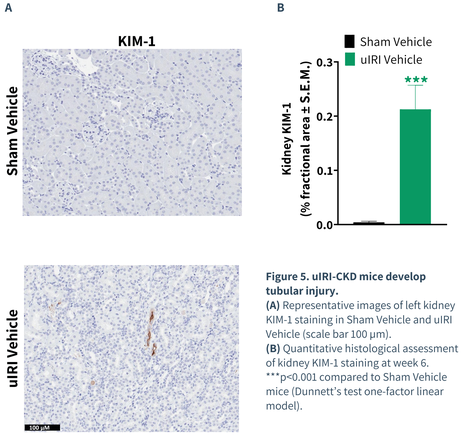


Figure 5. uIRI-CKD mice develop tubular injury.
(A) Representative images of left kidney KIM-1 staining in Sham Vehicle and uIRI Vehicle (scale bar 100 µm).
(B) Quantitative histological assessment of kidney KIM-1 staining at week 6. ***p<0.001 compared to Sham Vehicle mice (Dunnett's test one-factor linear model).

6 uIRI mice develops robust kidney fibrosis

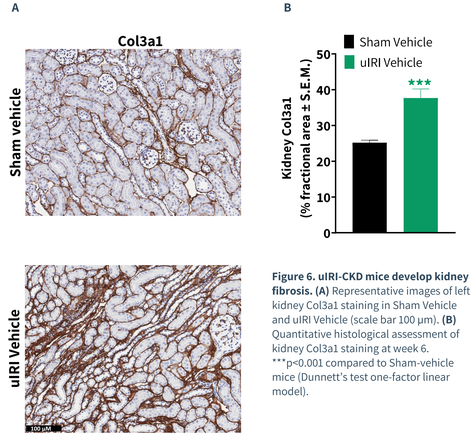


Figure 6. uIRI-CKD mice develop kidney fibrosis. (A) Representative images of left kidney Col3a1 staining in Sham Vehicle and uIRI Vehicle (scale bar 100 µm). **(B)** Quantitative histological assessment of kidney Col3a1 staining at week 6. ***p<0.001 compared to Sham-vehicle mice (Dunnett's test one-factor linear model).

CONCLUSION

The uIRI mouse model of CKD demonstrates:

+ Increased plasma markers of kidney injury
+ Kidney inflammation
+ Kidney tubular injury
+ Robust kidney fibrosis

The uIRI mouse model is a translational preclinical model suitable for testing novel drug therapies for CKD.

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