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Sex-driven Differences in the Renal Injury Severity and Recovery During AKI-to-CKD Transition

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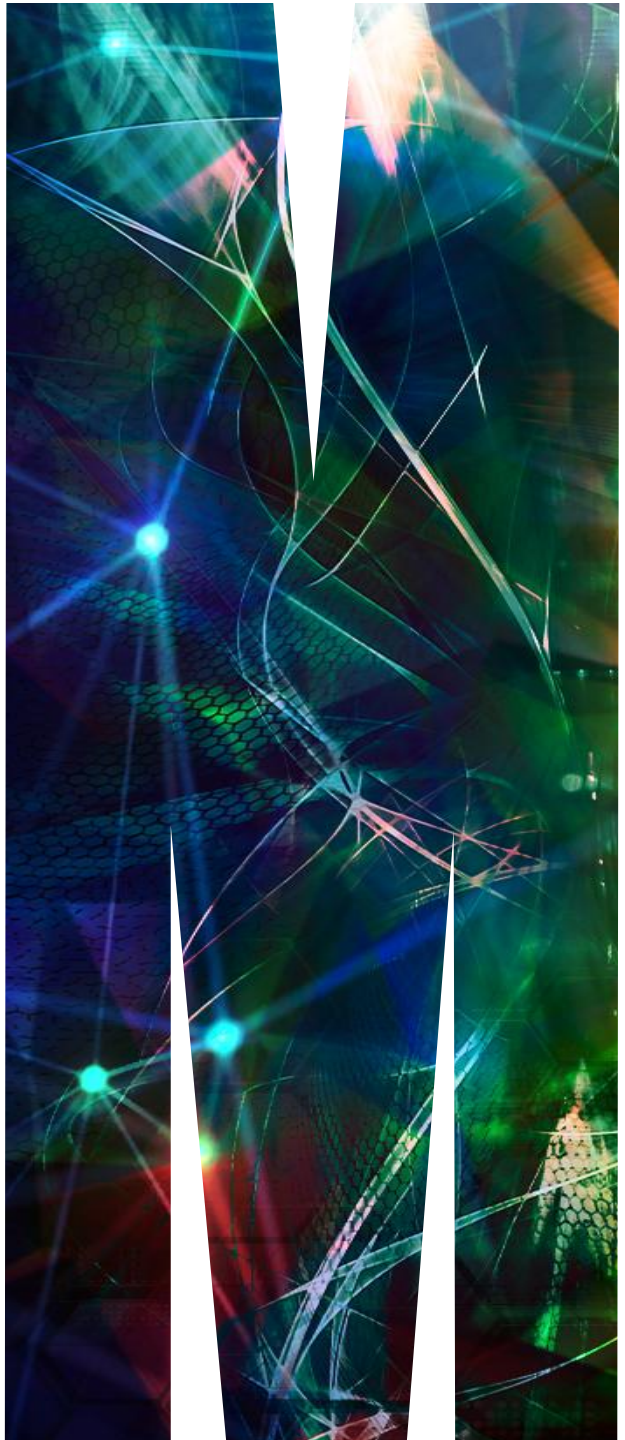
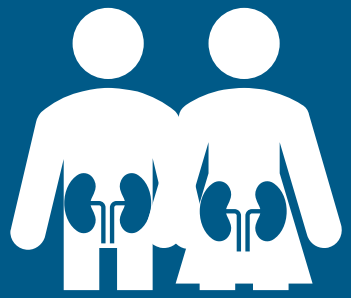


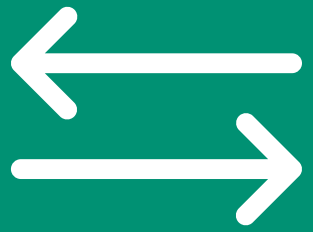
Sex-driven Differences in AKI-to-CKD Transition

Challenges



- Different incidence and severity of kidney disease between male vs. female[1,2]

What is known



- Interconnection between AKI and CKD[3]
- Females show protective mechanism[4]
- Not only estrogen involved[4]

Knowledge gap

- Limited information on AKI-to-CKD transition
- Sex-dependent progression mechanisms remain unclear

1. Carrero JJ et al, *Nat Rev Nephrol* 2018 Mar;14(3):151-164.
2. Stallard BC, McDonald SP. *Am J Nephrol*, 2025
3. Zhang T et al, *Am J Physiol Renal Physiol*, 2024 Nov 1;327(5):F788-F805.
4. Tonnus W et al, *Nature*, 2025

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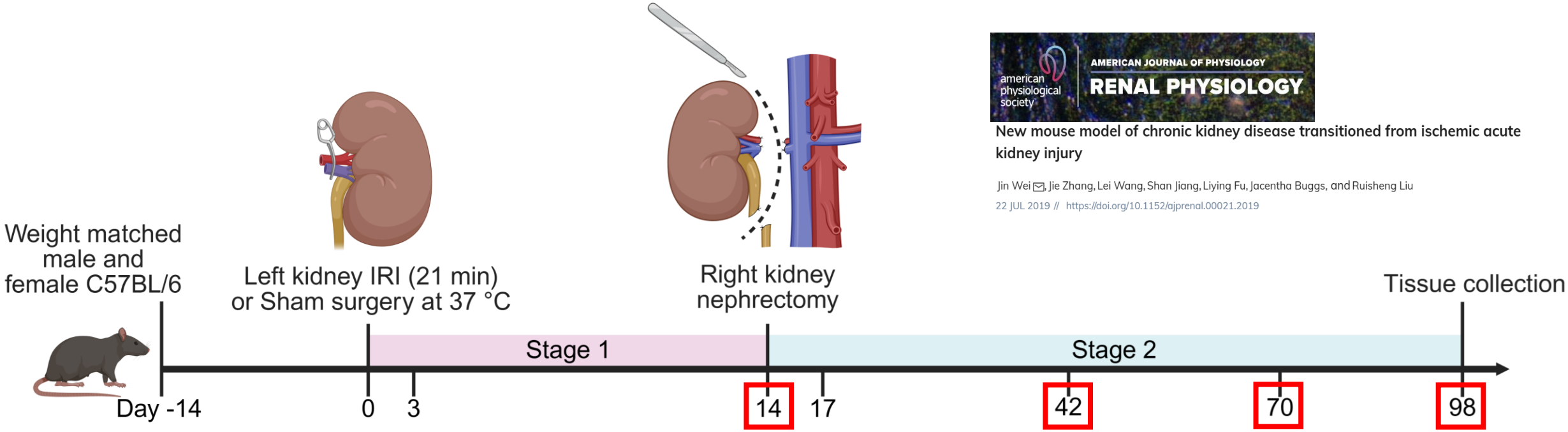
Aim: To investigate sex-driven differences in renal injury severity and recovery during AKI-to-CKD



New mouse model of chronic kidney disease transitioned from ischemic acute kidney injury

Jin Wei ✉, Jie Zhang, Lei Wang, Shan Jiang, Liying Fu, Jacentha Buggs, and Ruisheng Liu

22 JUL 2019 // https://doi.org/10.1152/ajprenal.00021.2019

- Kidney function: transdermal GFR (FITC-sinistrin); urinary KIM-1/creatinine ratio; uACR
- Histopathology - PAS and Picrosirius Red staining (PSR)
- Immunohistochemistry staining: KIM-1 and immune markers

Wei J, et al. *Am J Physiol Renal Physiol.* 2019

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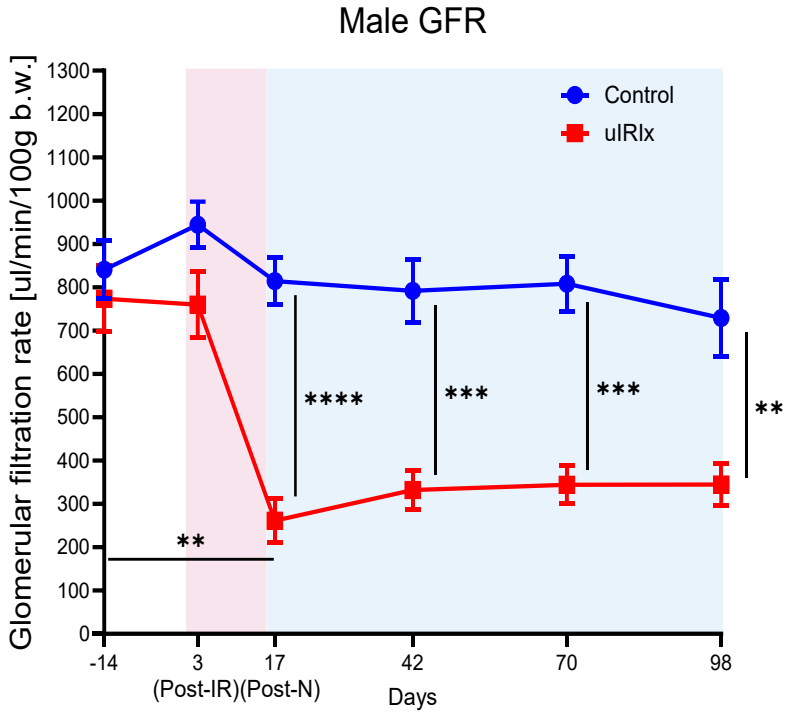
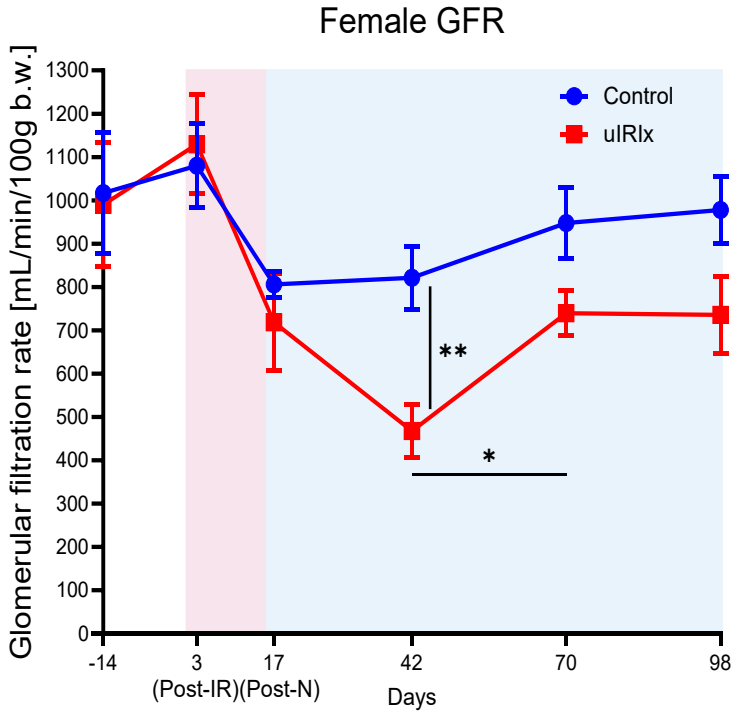
Kidney function

KIM-1/Creatinine ratio & Glomerular filtration rate





- Male uIRIx showed consistently decreased GFR, female mice only showed decreased GFR at day 42.
- uACR and urine output indicated severe injury in male mice.

Mean ±SEM; n=5-6, Two-way ANOVA and mixed-effects model with Tukey's post hoc test

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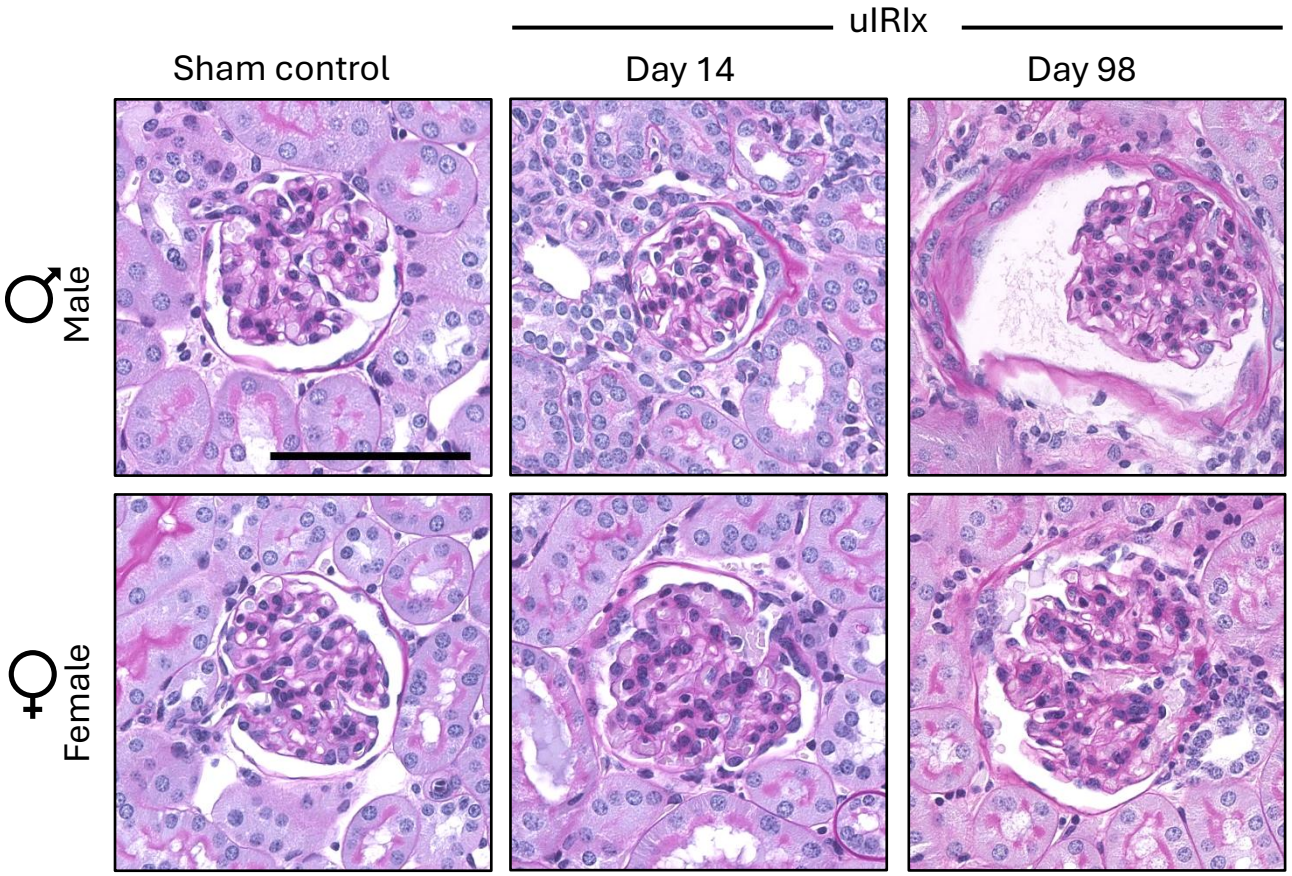
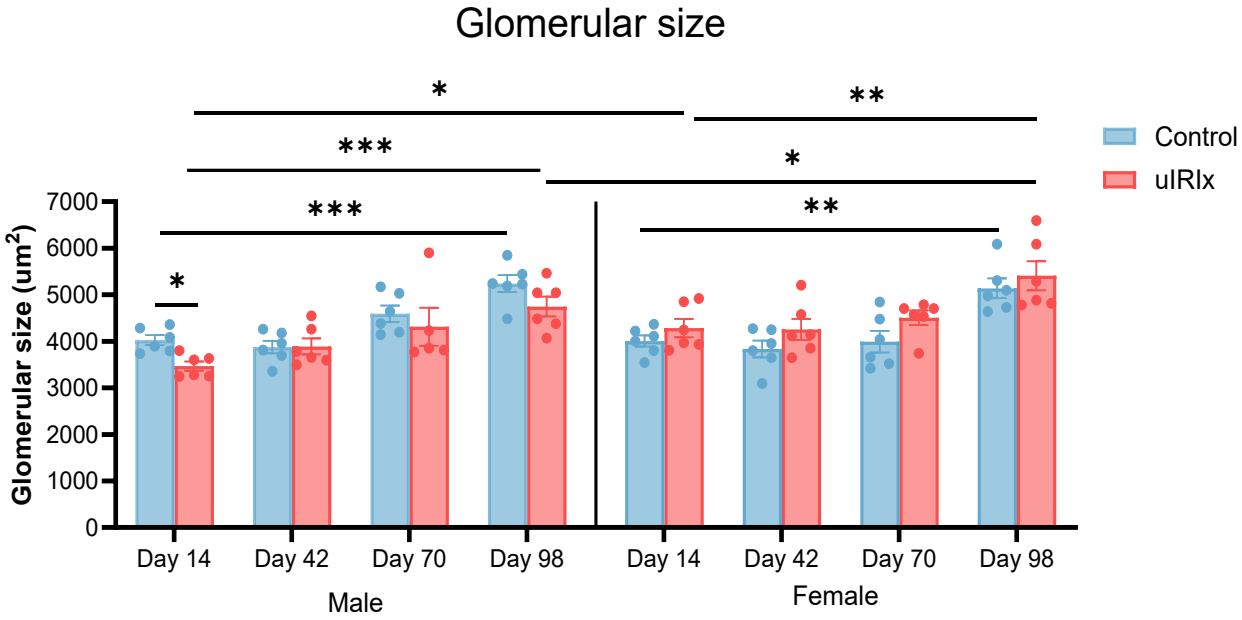
Glomerular hypertrophy





- At day 14, uIRIx male mice exhibited reduced glomerular size vs. sham controls and injured female.
- By day 98, glomeruli of uIRIx males remained smaller than uIRIx female mice.

Mean ±SEM; n=5-6, Two-way ANOVA, scale bar=100μm

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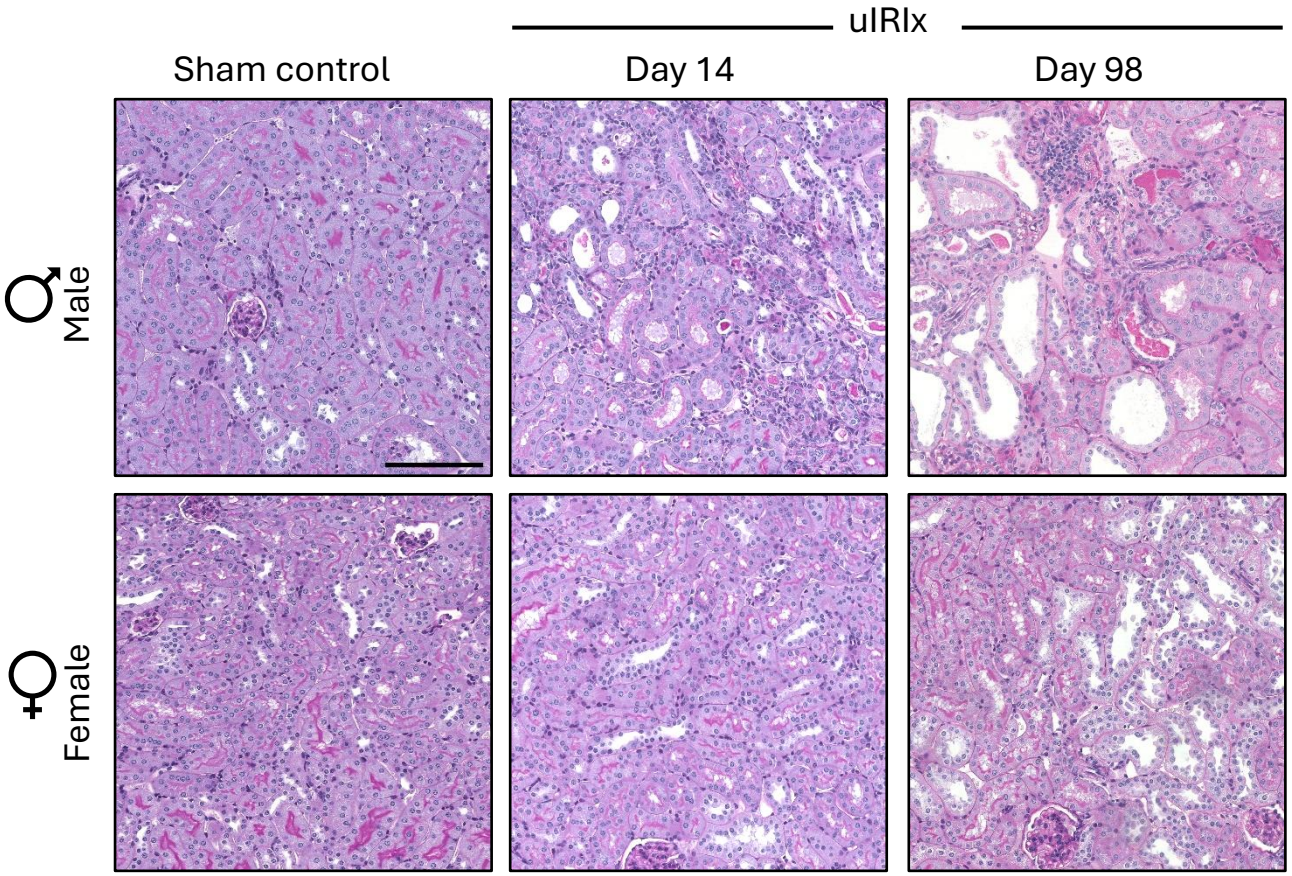
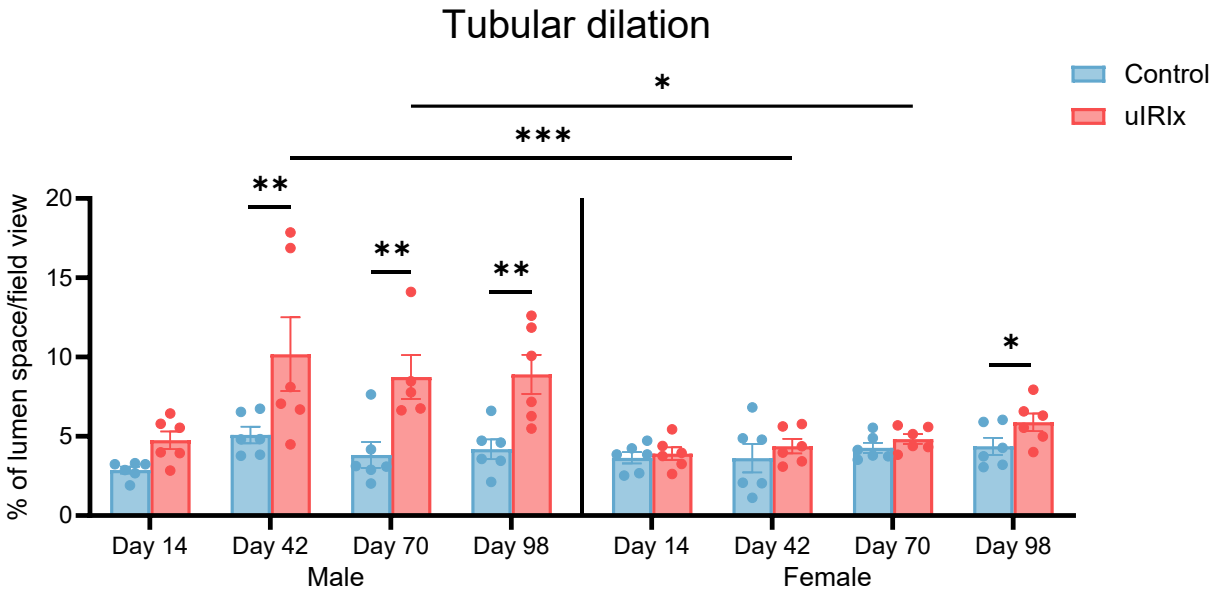
Tubular dilation





- Mice uIRIx mice showed tubular dilation from > day 42.
- Tubular dilation was only observed at 98-day post-uIRIx in females.

Mean ±SEM; n=5-6, Two-way ANOVA, scale bar=150μm

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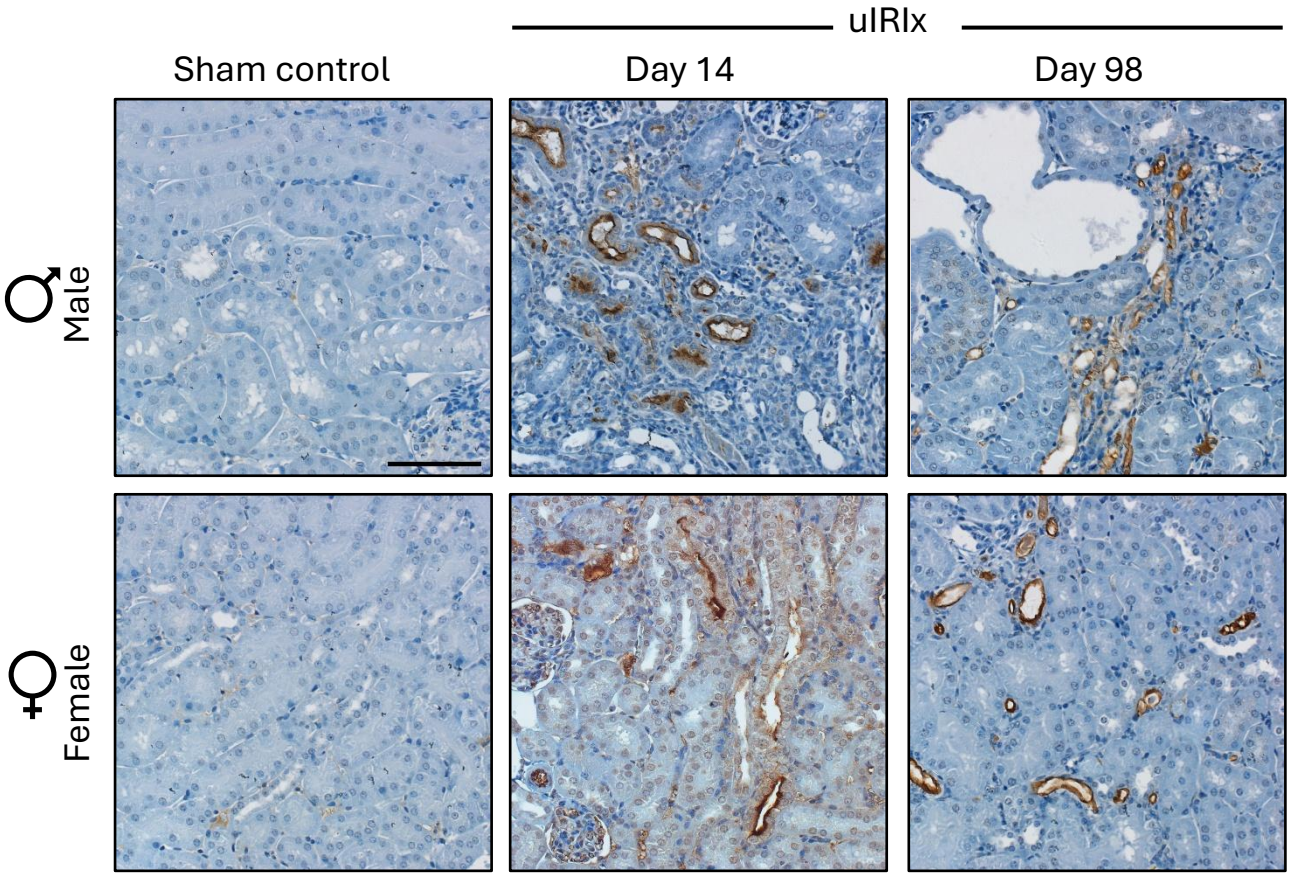
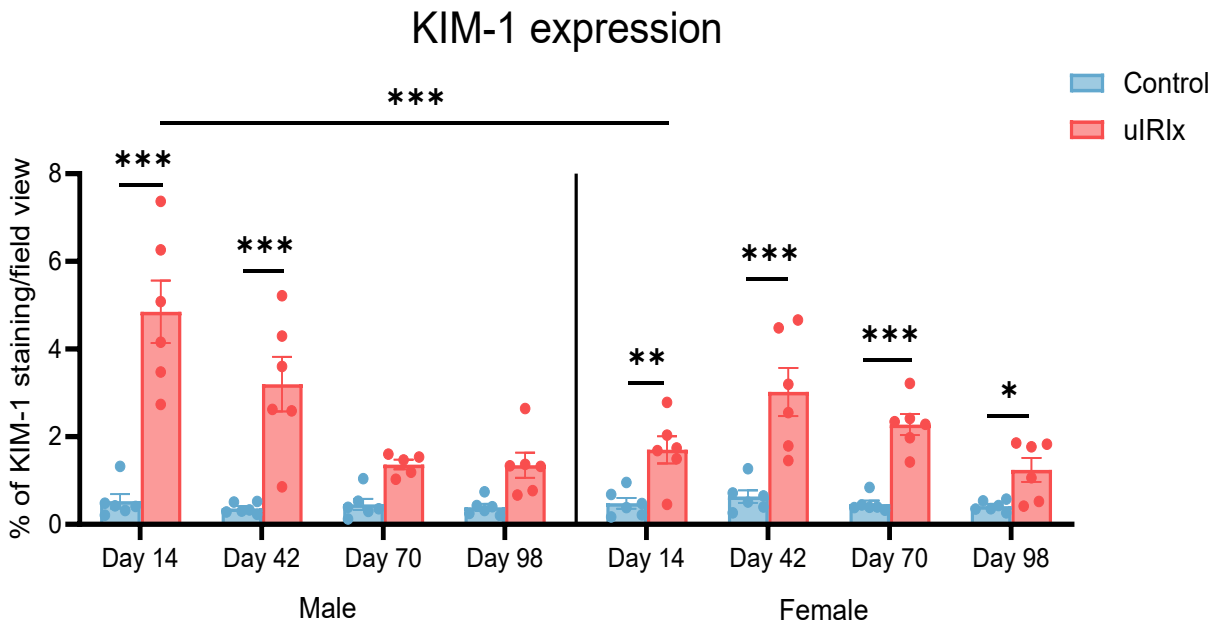
Immunohistochemistry

Kidney Injury Molecule (KIM-1)





- Male uIRIx mice showed increased KIM-1 expression at day 14 and 42.
- Female uIRIx mice showed increased KIM-1 expression but lower than that in males at day 14.

Mean ±SEM; n=5-6, Two-way ANOVA, scale bar=100μm

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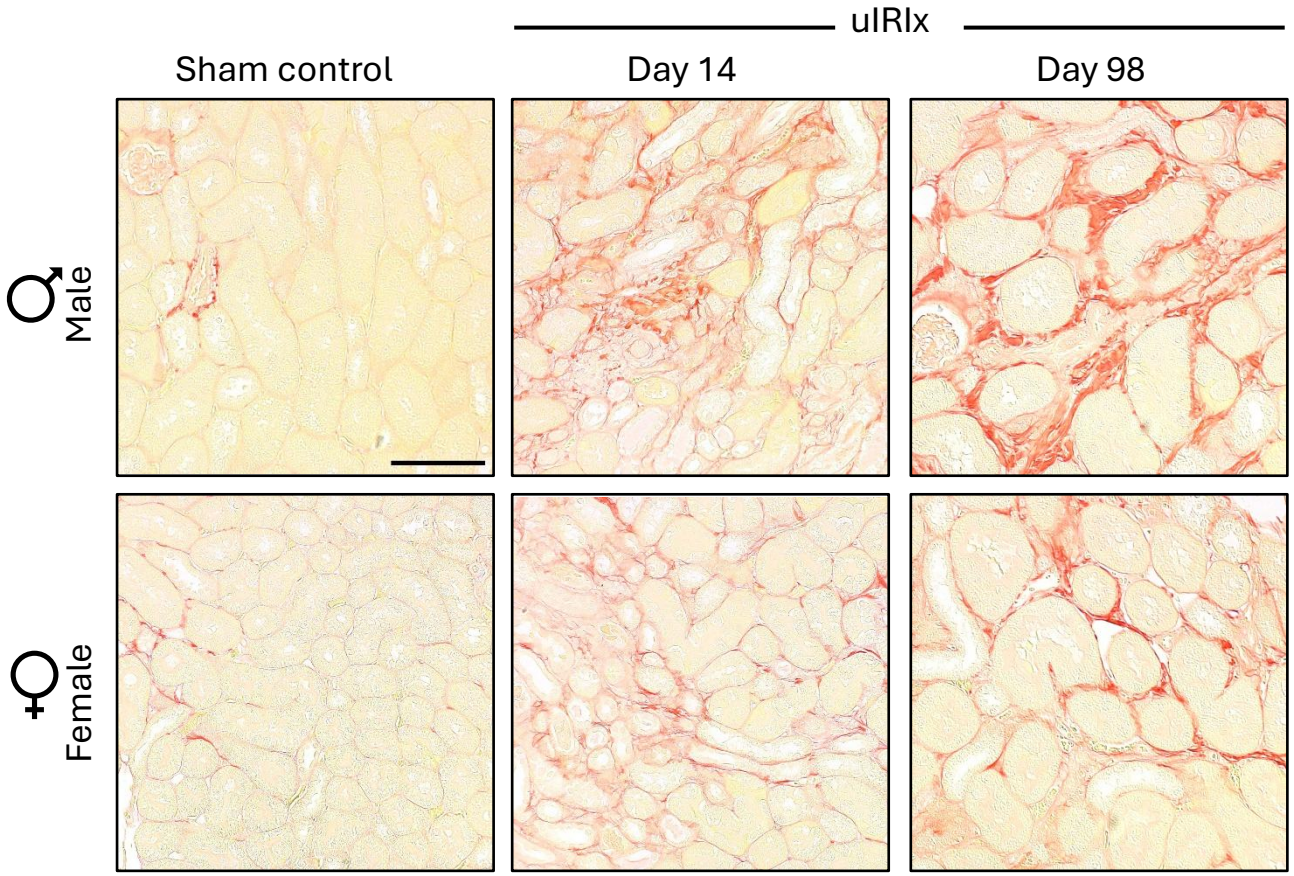
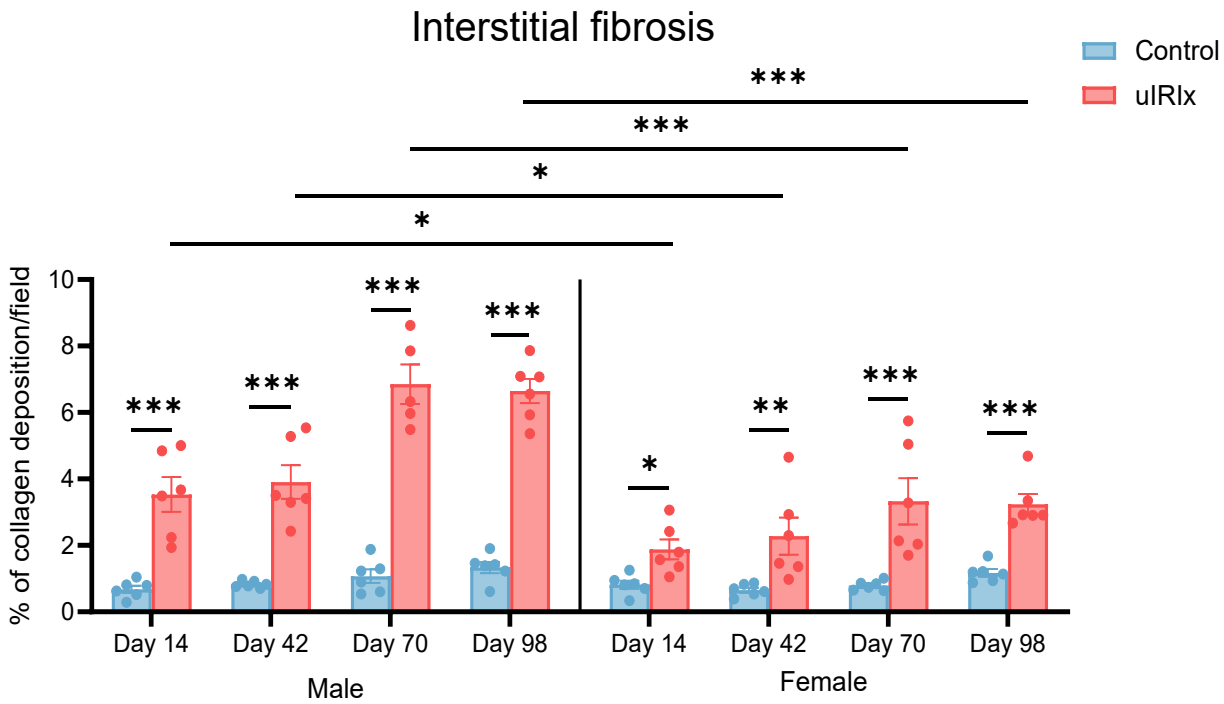
Accumulation of collagen

Picrosirius Red staining





- uIRIx mice showed significantly greater fibrosis vs. sham controls at all timepoints.
- Progressive accumulation from day 14 to day 70 and remained similar level by day 98.

Mean ±SEM; n=5-6, Two-way ANOVA, scale bar=100μm

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Summary

Sex	Findings in AKI-to-CKD transition
Male ♂	↑ Tubular injury ↑ Fibrosis accumulation ↓ Glomerular size ↓ Kidney function
Female ♀	↓ Tubular injury ↓ Fibrosis accumulation ↑Glomerular size Partial recovery of kidney function

Ongoing studies: investigating inflammatory responses (F4/80;CD3) and capillary rarefaction (CD31) in AKI-to-CKD transition.

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