

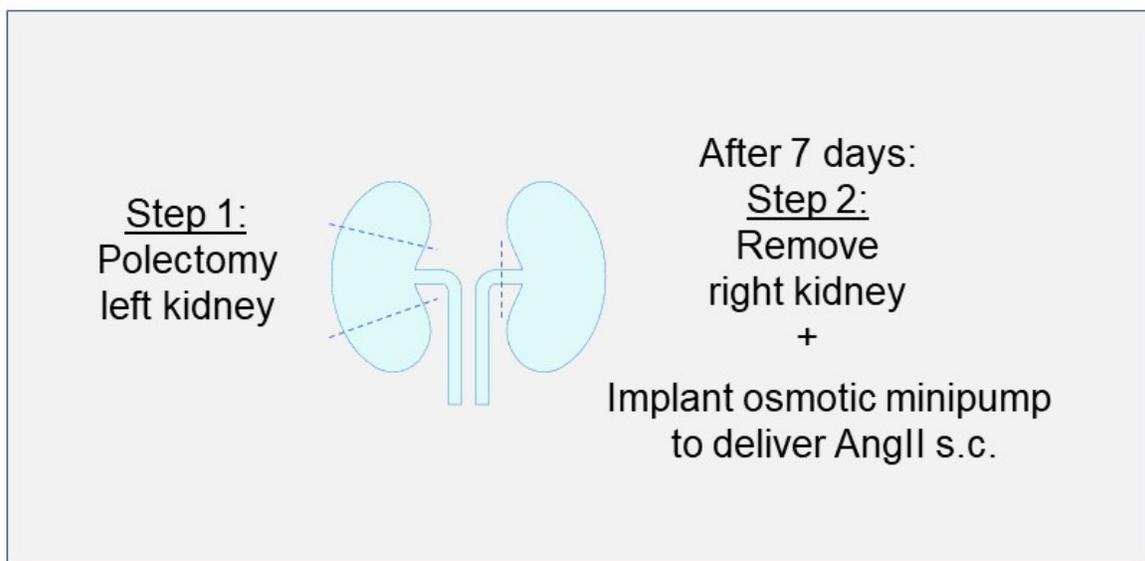
A chronic kidney disease (CKD) model in C57Bl/6 mice

In the **Renal Physiology Sub-Core of Core B Pre-clinical Studies of AKI**, Dr. Volker Vallon's laboratory has established a chronic kidney disease (CKD) model in C57Bl/6 mice as described below.

Making C57BL/6 mice susceptible to subtotal nephrectomy-induced CKD

Many gene-targeted mouse models are on a C57BL/6 background, a mouse strain that is notoriously resistant to developing hypertension and CKD in response to experimental models that reduce kidney mass by tissue resection.

Core B has now established a mouse model that converts the C57BL/6 mouse strain from being CKD resistant in response to subtotal nephrectomy (STN) to “CKD susceptible” – this is achieved by co-infusing angiotensin II. The latter mimics the blood pressure increase observed in other mouse strains that are susceptible to CKD following STN. The approach is adapted from the original description by Leelahavanichkul et al (1). Briefly, one week after polectomy of the left kidney, the right kidney is removed and an osmotic minip



ump is implanted subcutaneously to deliver angiotensin II (AngII: 0.75 $\mu\text{g}/\text{kg}/\text{min}$)(see **Figure 1**). Sham mice receive the same two episodes of anesthesia and surgery and kidney manipulations except that no polectomy or heminephrectomy is performed and no minipump implanted.

Figure 2 shows the renal and blood pressure phenotype in STN+AngII vs sham mice. The model increases systolic blood pressure - measured by a computerized tail-cuff system in awake mice at 5 weeks after the last surgery. GFR, measured one week later in awake mice by FITC-sinistrin plasma elimination kinetics, reveals a robust reduction in GFR. In week 7 after the last surgery, plasma, urine, heart and kidneys were collected. Plasma FGF23 is significantly elevated in the CKD model. A marked increase in urinary albumin to creatinine ratios (UACR) is observed and associated with an increase in glomerular injury score - assessed by a renal

pathologist blinded to study groups. Robust increases in renal mRNA expression of CCL2, KIM-1, NGAL, TIMP1 and COL1A1 in the CKD model indicate inflammation, injury, and fibrotic processes that are associated with significantly higher Masson's trichrome collagen staining (investigator blinded to study groups).

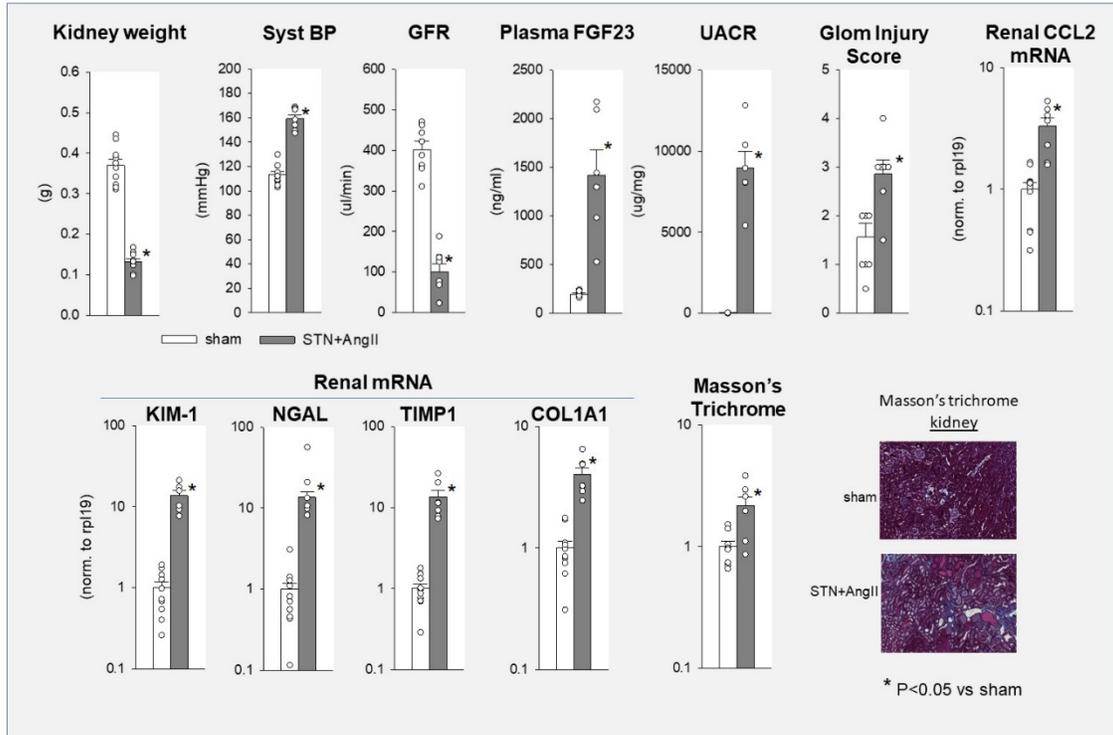
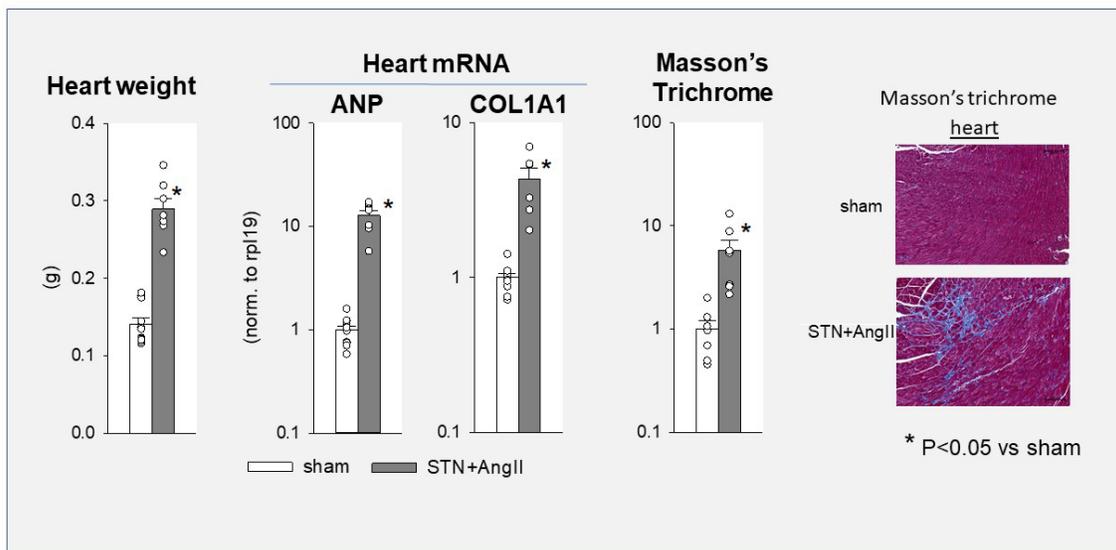


Figure 3 shows that this CKD model also presents a robust cardiac phenotype, as indicated by significantly higher heart weight, heart ANP and COL1A1 mRNA expression as well as Masson's trichrome collagen staining.



References

- (1) Leelahavanichkul A, Yan Q, Hu X, Eisner C, Huang Y, Chen R, Mizel D, Zhou H, Wright EC, Kopp JB, Schnermann J, Yuen PS, Star RA. Angiotensin II overcomes strain-dependent resistance of rapid CKD progression in a new remnant kidney mouse model. *Kidney Int.* 2010 Dec;78(11):1136-53.