Sparsentan Improves Glomerular Endothelial and Podocyte Functions and Augments Protective Tissue Repair in a Mouse Model of Focal Segmental Glomerulosclerosis (FSGS)

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DISCLOSURES & ACKNOWLEDGMENTS

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Background

- Sparsentan is a novel, single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) being investigated for the treatment of FSGS.[1]

- Emerging evidence indicates strong nephroprotective actions of sparsentan, with more pronounced effects compared with the current standard of care using an ARB.[2,3]

- Previously, we reported antiproteinuric and protective hemodynamic effects of sparsentan in both FSGS and normal mouse kidneys and differences between sparsentan and AT_1R inhibition alone.[4]
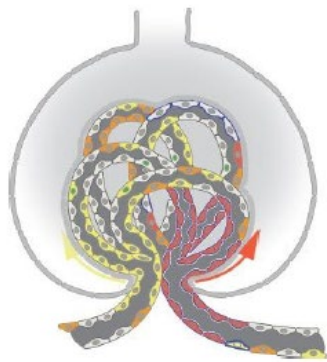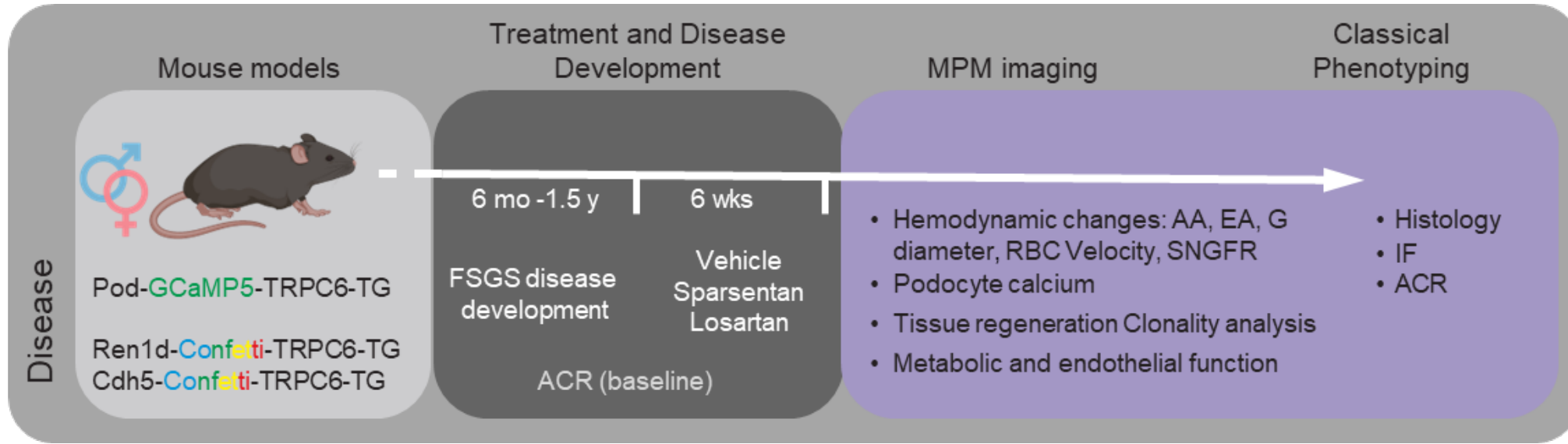
Aims

- Investigation of the glomerular cell and molecular mechanisms of sparsentan's protective effects in experimental FSGS, by direct visualization of effects in the intact living mouse kidney.

ARB, angiotensin receptor blocker; FSGS, Focal Segmental Glomerulosclerosis.
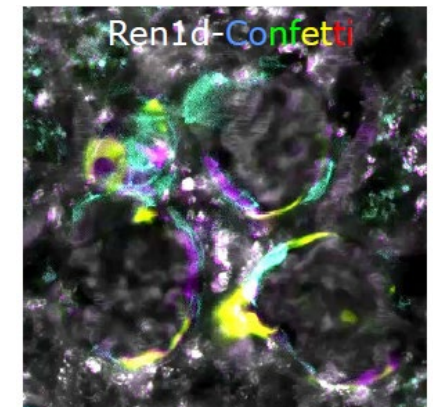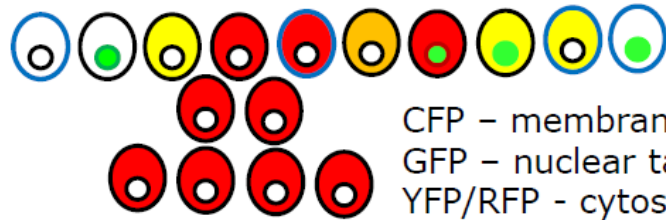**1.** Komers R, et al. *Kidney Int Rep*. 2020;5:494-502. **2.** Gyarmati G, et al. *Nephrol Dial Transplant*. 2021;36(suppl 1):i10. Abstract FC016.
3. Trachtman H, et al. *J Am Soc Nephrol*. 2018;29:2745-2754. **4.** Gyarmati G, et al. ERA-EDTA, June 5-8, 2021. Berlin.

Methods

Treatment and Disease Development

Mouse models

Disease

Pod-GCaMP5-TRPC6-TG

Ren1d-Confetti-TRPC6-TG
Cdh5-Confetti-TRPC6-TG

6 mo -1.5 y | 6 wks

FSGS disease development | Vehicle Sparsentan Losartan

ACR (baseline)

MPM imaging

- Hemodynamic changes: AA, EA, G diameter, RBC Velocity, SNGFR
- Podocyte calcium
- Tissue regeneration Clonality analysis
- Metabolic and endothelial function

Classical Phenotyping

- Histology
- IF
- ACR

Multicolor CFP/GFP/YFP/RFP reporter that allows single cell ID and fate tracking

CFP – membrane targeted
GFP – nuclear targeted
YFP/RFP - cytosolic

Cdh5-Confetti
Albumin –Alexa Fluor 680

Ren1d-Confetti

ACR, albumin:creatinine ratio; AA, afferent arteriole; Coef, coefficient; EA, efferent arteriole; FSGS, Focal Segmental Glomerulosclerosis; GSC, glomerular sieving coefficient; ns, not significant; pod, podocyte; RBC, red blood cell; SNGFR, single nephron GFR.

5. Kaverina NV, et al. *PLoS One*. 2017;12(3):e0173891. **6.** Desposito D, et al. *JCI Insight*. 2021;6(10):e123392.
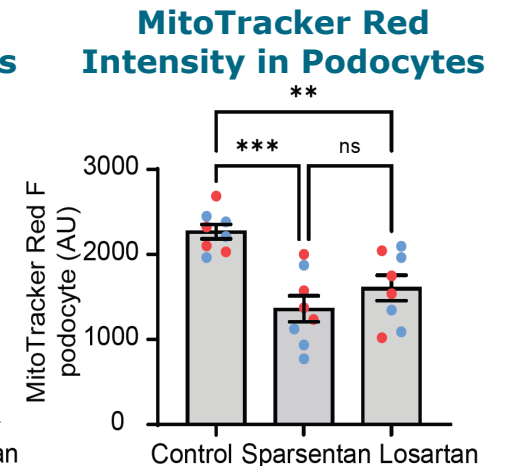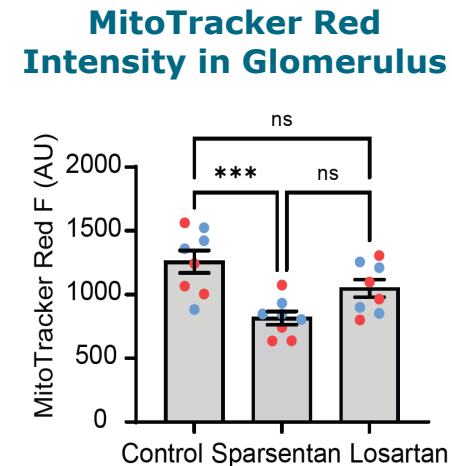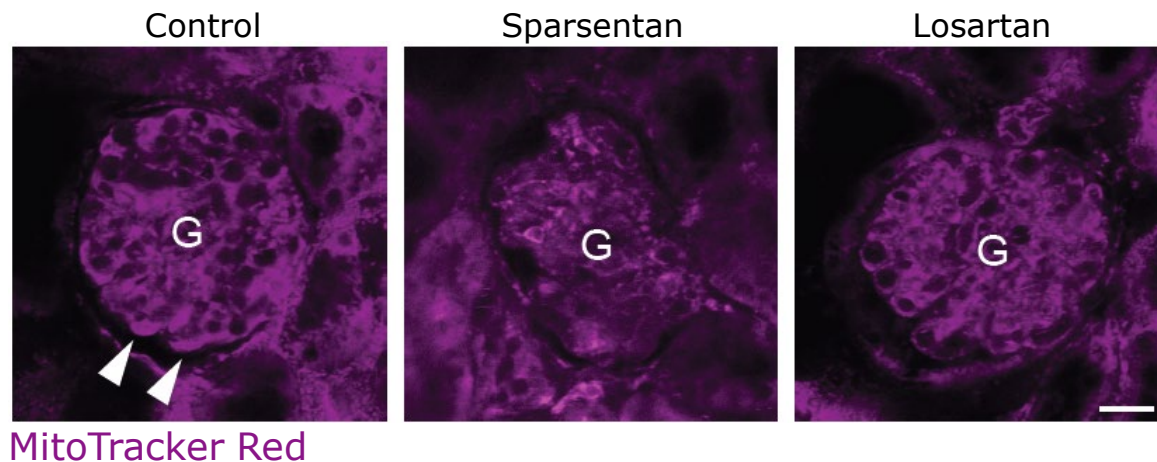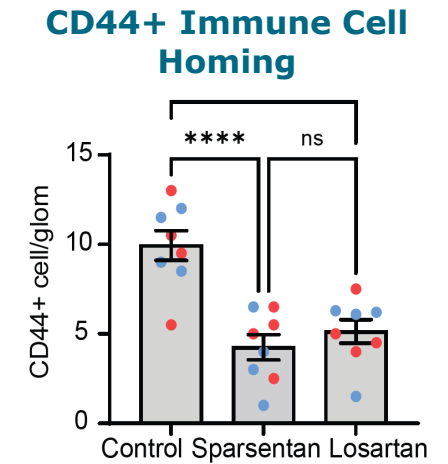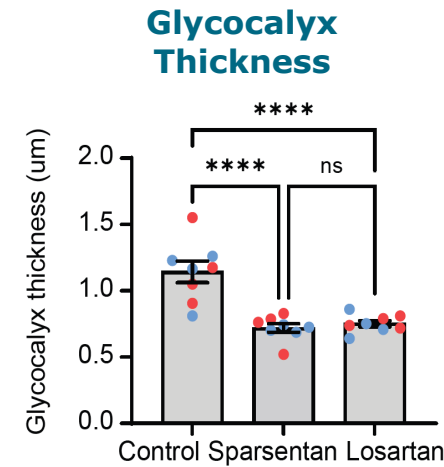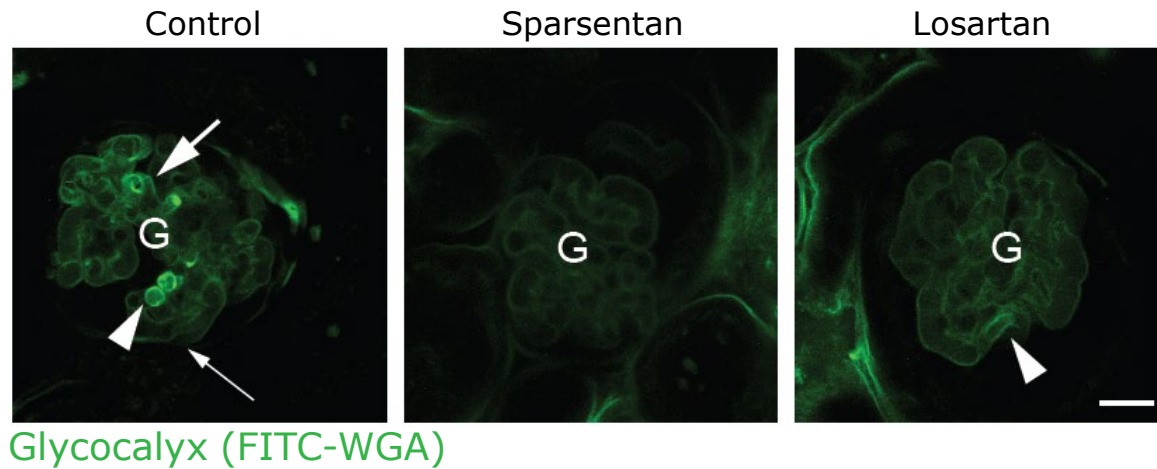
Effects of Sparsentan and Losartan on Glomerular Hemodynamics and GFB Function in FSGS
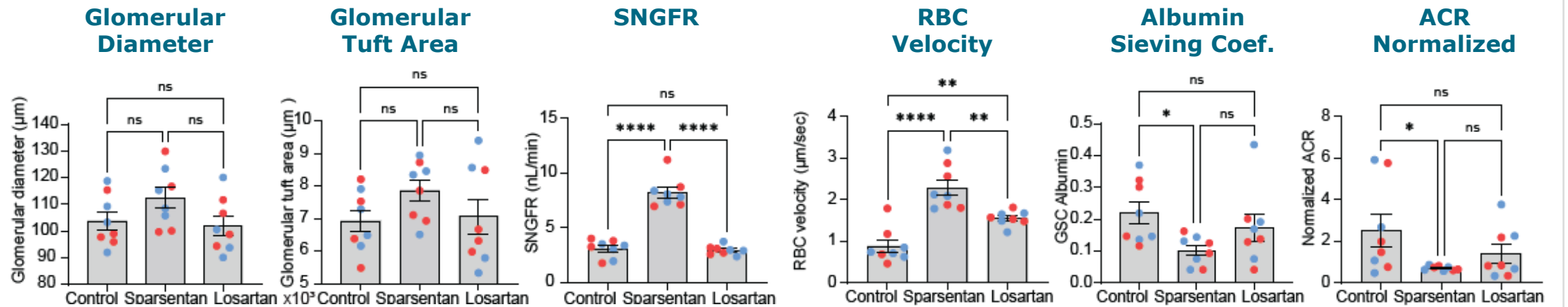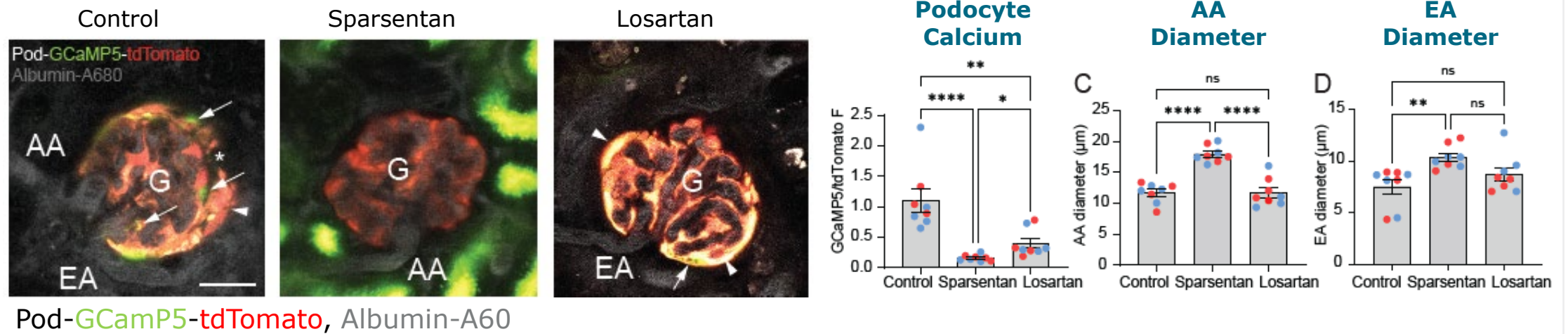
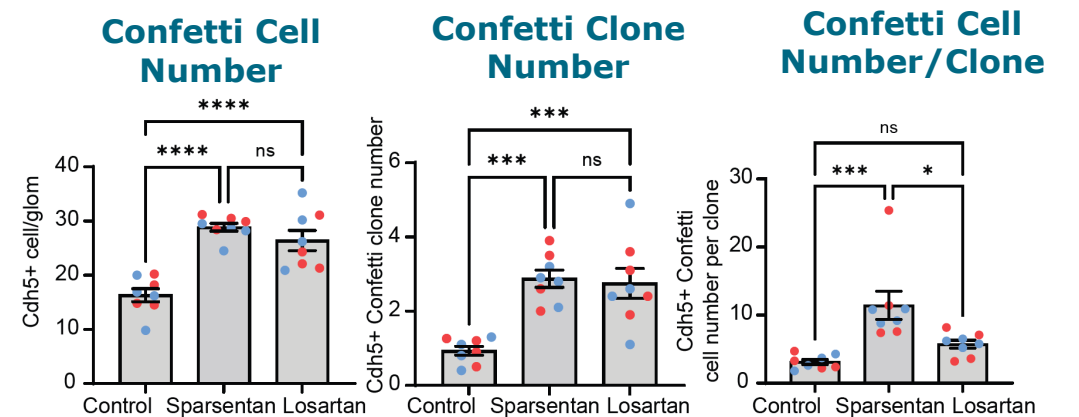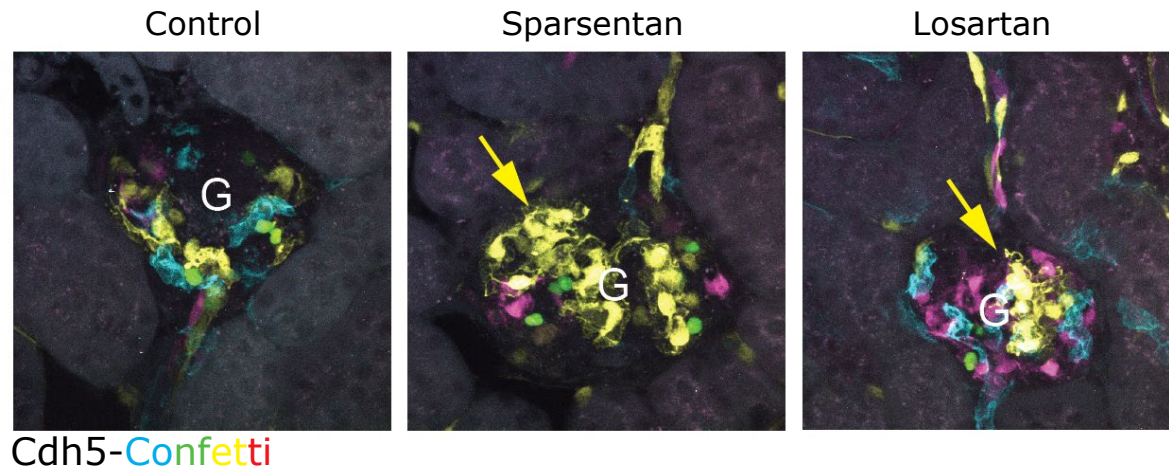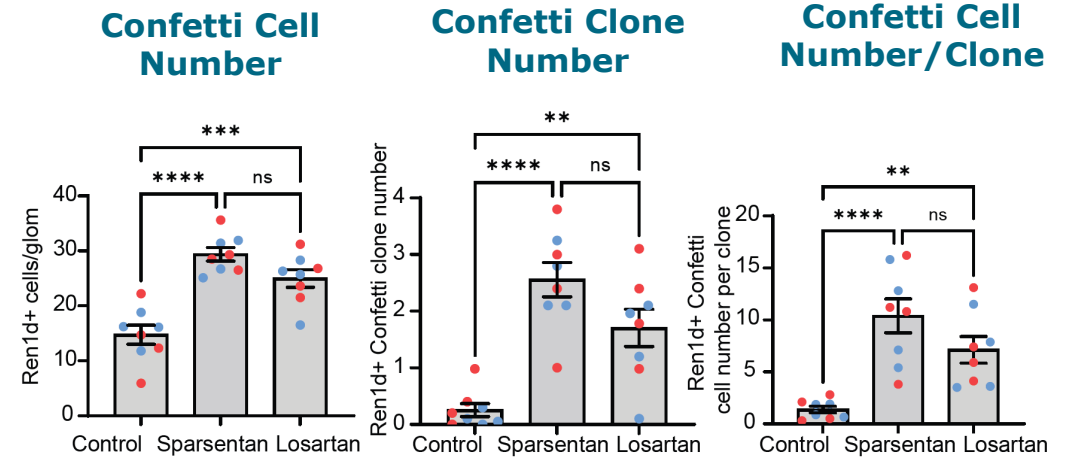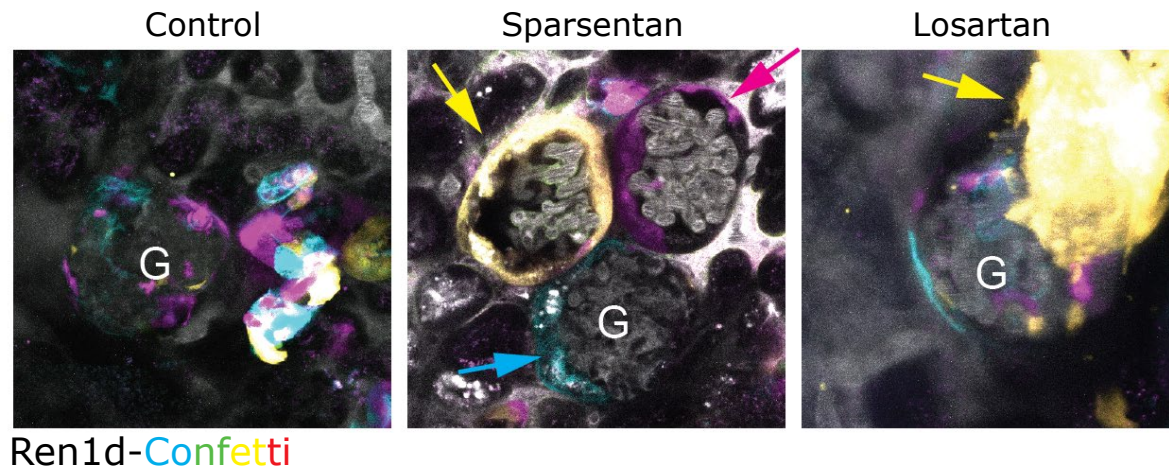Bars in microscopy images are 20 µm. Values are mean ± SEM. **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.
ACR, albumin:creatinine ratio; AA, afferent arteriole; Coef, coefficient; EA, efferent arteriole; GSC, glomerular sieving coefficient; ns, not significant; pod, podocyte; RBC, red blood cell; SNGFR, single nephron GFR; SEM, standard error of the mean.

Sparsentan Restored Glomerular Endothelial Glycocalyx and Attenuated Mitochondrial Stress and Immune Cell Homing

Bars in microscopy images are 20 μm. Values are mean ± SEM. **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.
G, glomeruli; ns, not significant; SEM, standard error of the mean.

Sparsentan Increased Endothelial and Renin Lineage Confetti+ Cells and Clones in Vasculature, Glomeruli and Tubules

Bars in microscopy images are 20 µm. Values are mean ± SEM. *$P<0.05$; **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.
G, glomeruli; ns, not significant; SEM, standard error of the mean.

Sparsentan improved glomerular hemodynamics, glomerular filtration barrier, and podocyte function

Multiphoton imaging in the intact living kidney of FSGS mice demonstrated underlying glomerular cell and molecular mechanisms of sparsentan's glomeruloprotective effects in experimental FSGS including:

- Attenuation of mitochondrial stress in podocytes
- Restoration of glomerular endothelial surface layer
- Reduction in CD44+ immune cell homing
- Enhanced endogenous tissue repair

Sparsentan was more effective than losartan at preserving kidney structure and function in the FSGS model, underscoring the importance of the endothelin component in the nephroprotective actions of sparsentan