



Sparsentan Protects the Glomerular Basement Membrane and Glycocalyx, and Attenuates Proteinuria in a Rat Model of Focal Segmental Glomerulosclerosis (FSGS)

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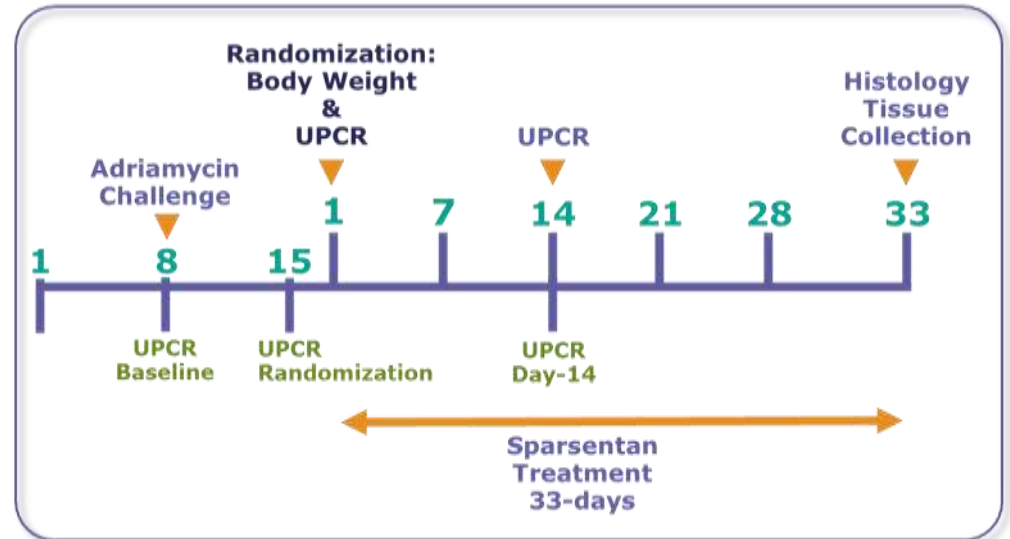
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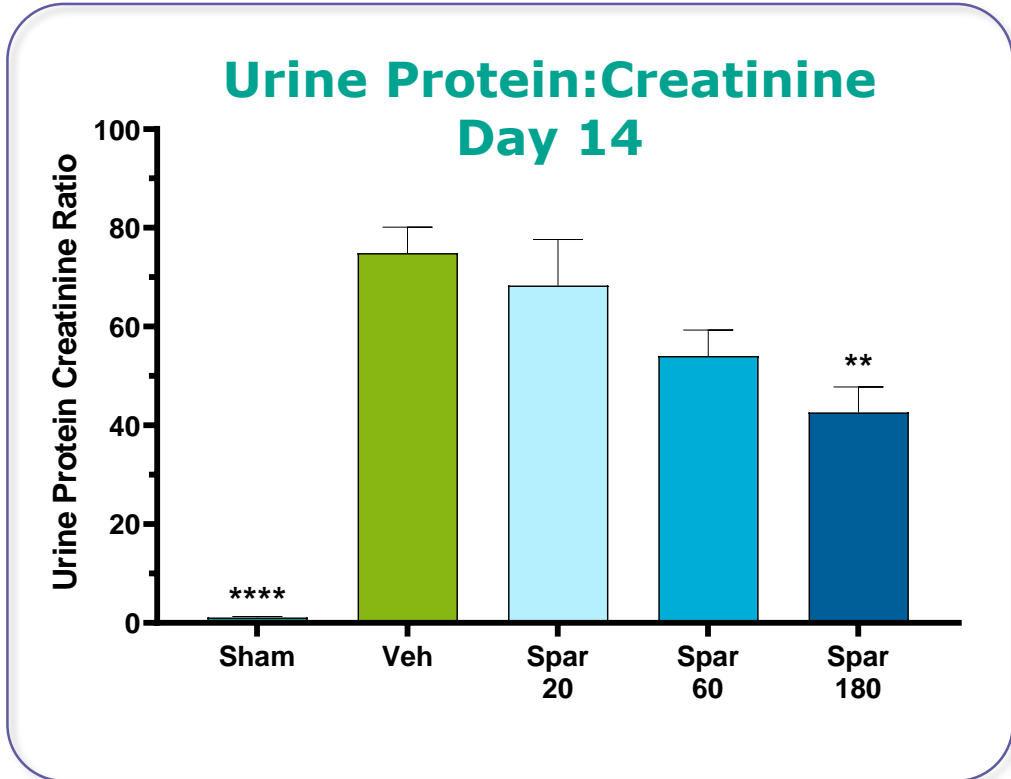
Introduction and Brief Methods

- Sparsentan is a novel, dual acting, highly selective antagonist of the **endothelin type A** and the **angiotensin II subtype 1** receptors.
- This first in class **Dual Endothelin Angiotensin Receptor Antagonist (DEARA)** is being investigated in phase 3 clinical trials for FSGS and IgA nephropathy.
- The Adriamycin rat model was used to **assess the ability of sparsentan to attenuate kidney injury** in an experimental FSGS setting.

- Male Sprague Dawley Rats
- 11-13 weeks old at start
- 5 mg/kg Adriamycin
 - Single IV injection
- Sparsentan treatment started 8-days after Adriamycin challenge
- Sham = No Adriamycin
- Vehicle = Adriamycin, no treatment

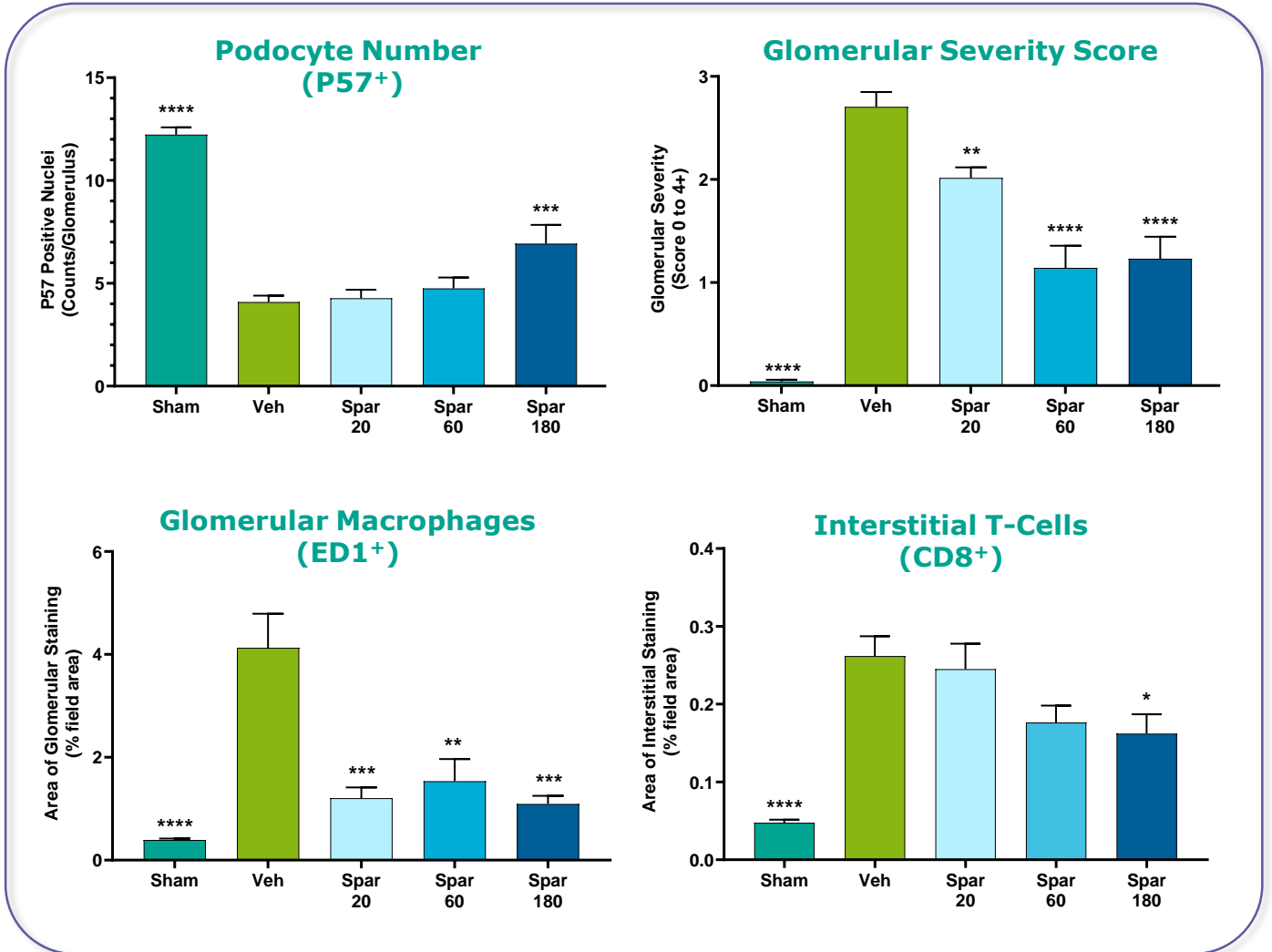


Urine protein:creatinine ratio and other disease pathologies positively impacted by sparsentan treatment



****p<0.0001, **p=0.0019

- Reduction in measures of disease pathology corresponded with attenuation of proteinuria

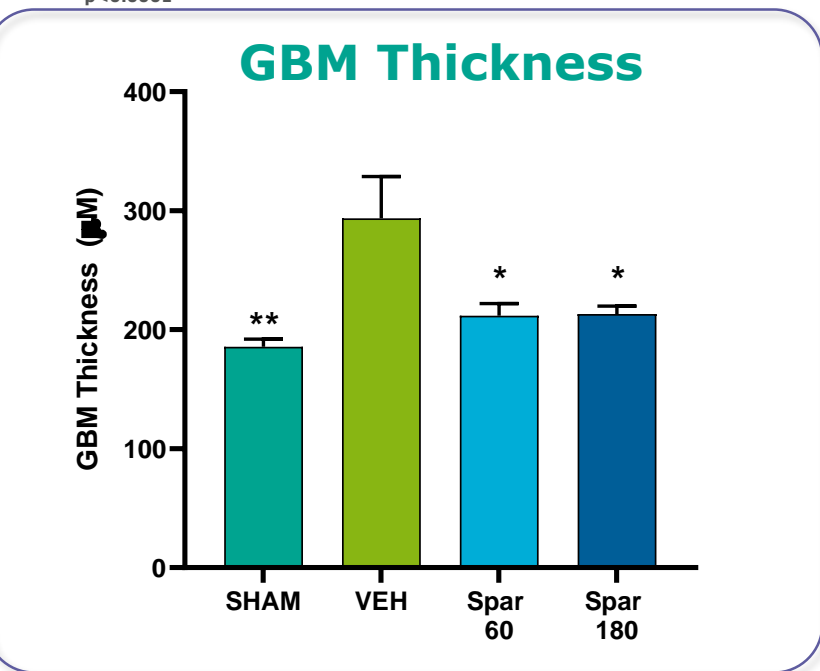
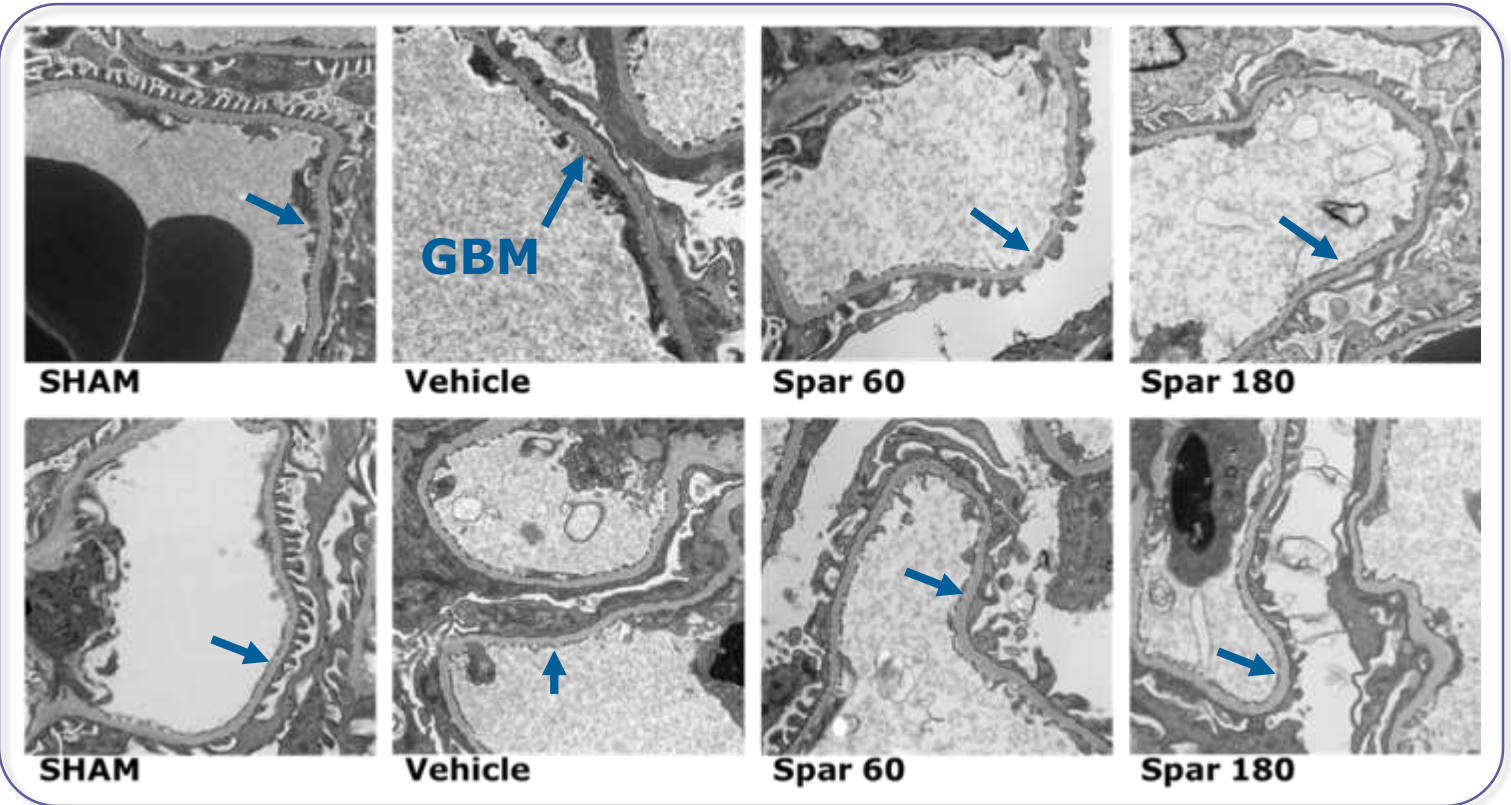
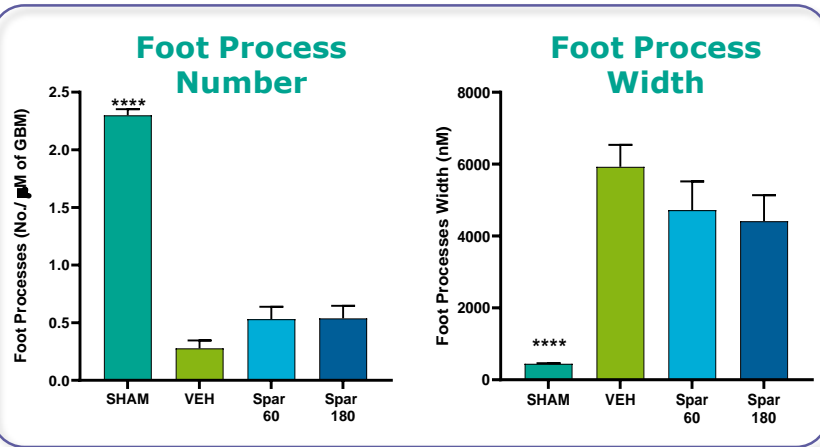


****p<0.0001, ***p≤0.001, **p<0.01, *p<0.05



Spar60 = sparsentan 60 mg/kg; Spar180 = sparsentan 180 mg/kg; VEH= Vehicle (Adriamycin, no treatment). One-way ANOVA, Dunnett's multiple comparisons, comparing all groups to Vehicle

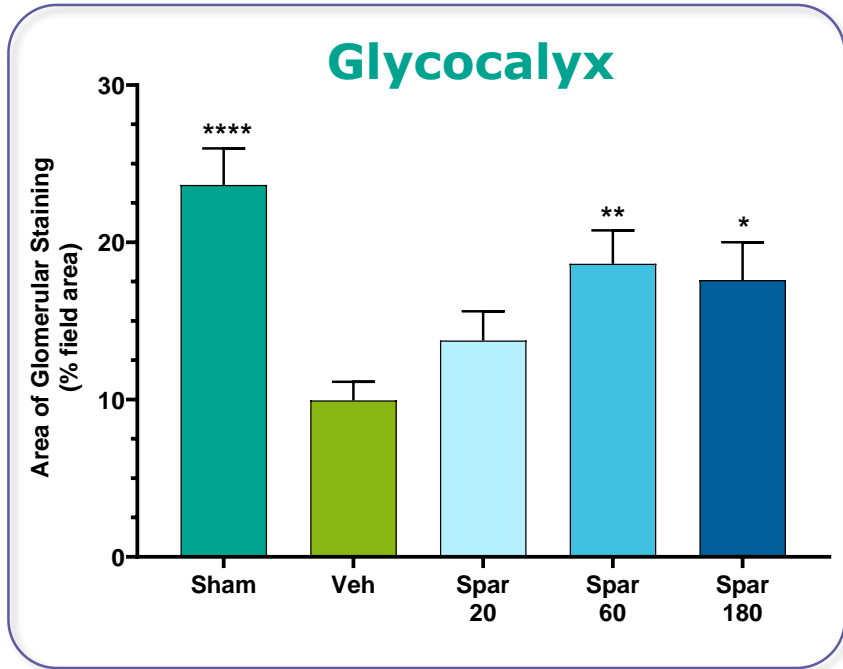
Glomerular basement membrane thickening at Day-33 was attenuated by sparsentan treatment (mean ± SEM)



- Representative electron microscopy images
- There was a trend in improvement in FP width and number in spar-treated animals
- Glomerular basement membrane (GBM) blue arrow →

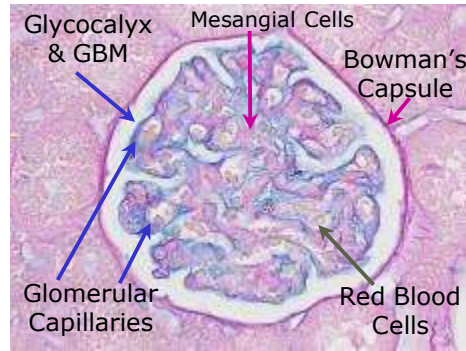
Spar60 = sparsentan 60 mg/kg; Spar180 = sparsentan 180 mg/kg; VEH= Vehicle (Adriamycin, no treatment). One-way ANOVA, Dunnett's multiple comparisons, comparing all groups to Vehicle.

Glomerular glycocalyx reduction at Day-33 was attenuated by sparsentan treatment (mean ± SEM)

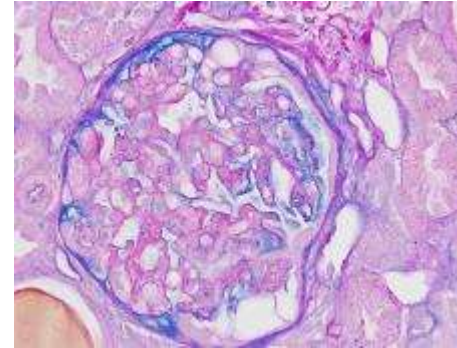


*p=0.0112, **p=0.0079, ****p<0.0001.

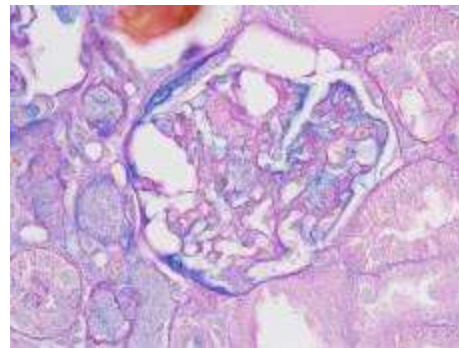
- Average of 25 glomeruli/animal
- Colloidal iron staining



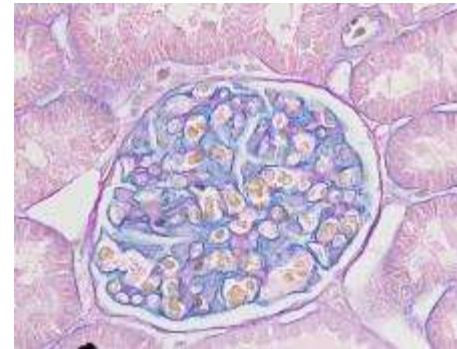
Sham



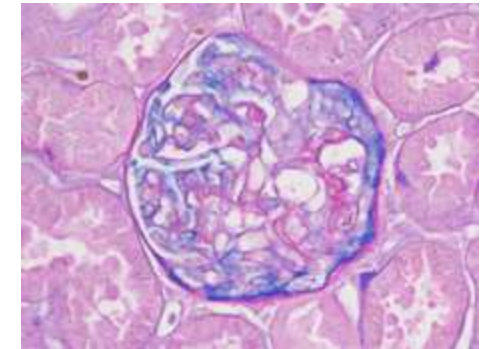
Vehicle



Spar 20mg/kg



Spar 60mg/kg



Spar 180 mg/kg

Blue:
glycocalyx mucins

Fuchsia:
collagen

Spar60 = sparsentan 60 mg/kg; Spar180 = sparsentan 180 mg/kg; VEH= Vehicle (Adriamycin, no treatment).
One-way ANOVA, Dunnett's multiple comparisons, comparing all groups to Vehicle

Conclusions

- Dual antagonism of **endothelin type A** and the **angiotensin II subtype 1 receptors** by sparsentan attenuated the development of renal functional and structural changes in rat ADR model of FSGS.
- Sparsentan treatment impacted multiple pathological disease features of the model including:
 - Attenuation of increase in **urine protein:creatinine**
 - Attenuation of **podocyte loss**
 - Maintenance of **glomerular basement membrane width**
 - Protection of **glycocalyx**
 - Reduction in **glomerular macrophage infiltration**

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