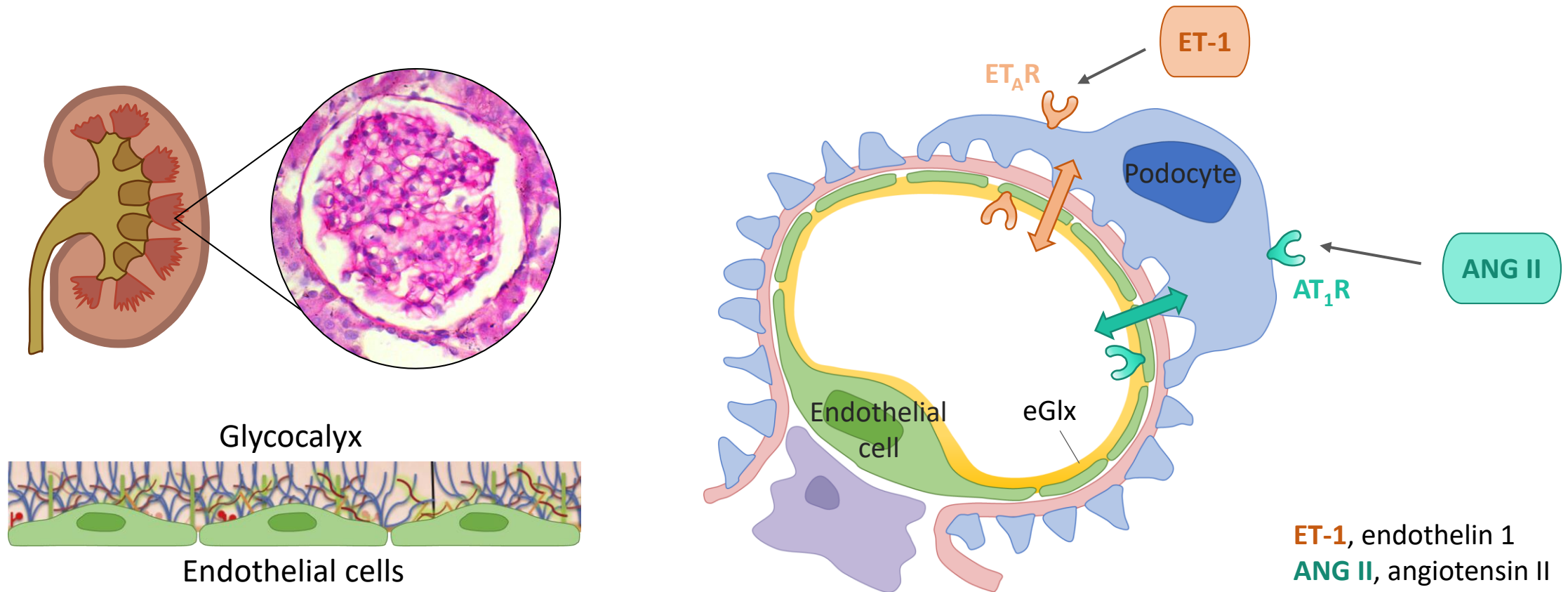


Sparsentan has direct effects on the glomerular capillary wall to attenuate increased permeability after exposure to nephrotic syndrome plasma

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Endothelin type A (ET_AR) and angiotensin II type 1 (AT₁R) receptors may regulate glomerular endothelial glycocalyx (eGlx)

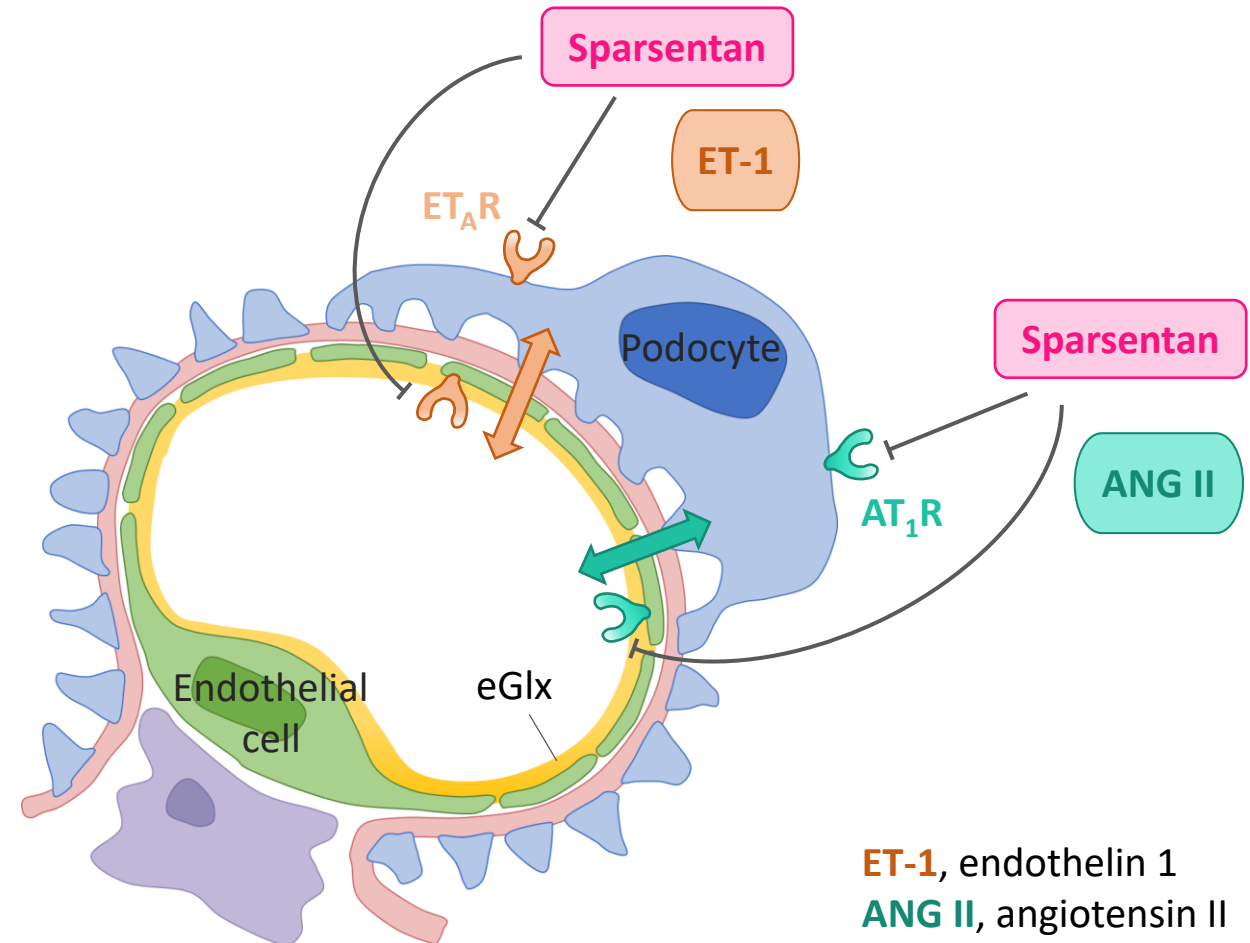


Daehn et al., 2014, PMID: 24590287; Ebefors et al., 2019, PMID: 31402170;
Kuwabara et al., 2010, PMID: 20526760; Crompton et al., 2023, PMID: 36749631

Sparsentan is a single molecule, dual ET_AR and AT₁R antagonist and therefore has potential to protect glomerular eGlx

Sparsentan

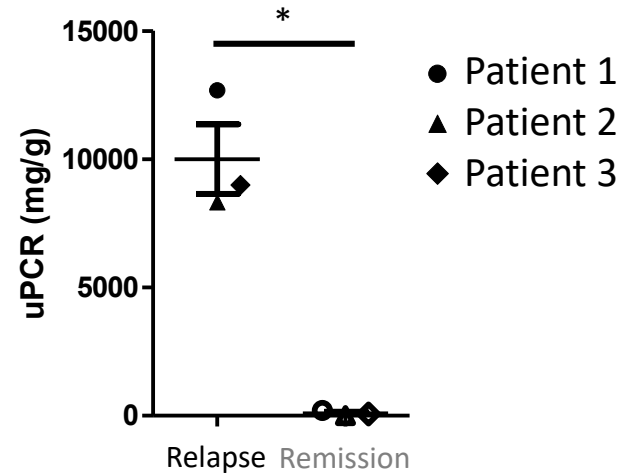
- Approved in US and EU for the reduction of proteinuria in adults with IgA nephropathy*
- Under clinical development for FSGS



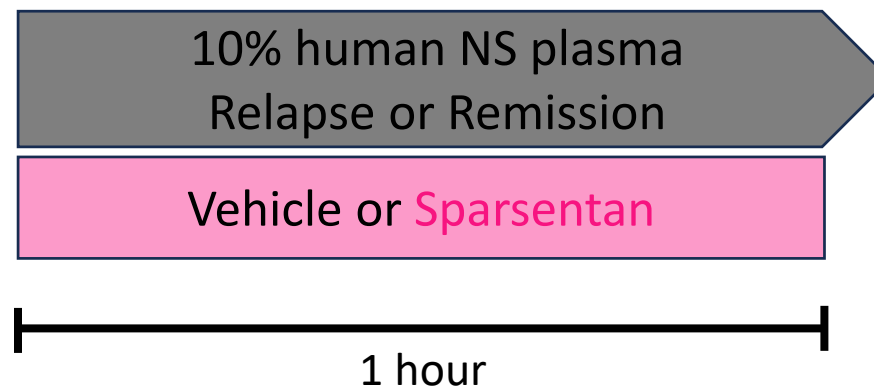
*accelerated approval in US; conditional approval in EU

AIM: Can sparsentan protect the eGlx and maintain the glomerular filtration barrier in rat glomeruli exposed to human nephrotic syndrome (NS) plasma?

Paired relapse/remission
human NS plasma

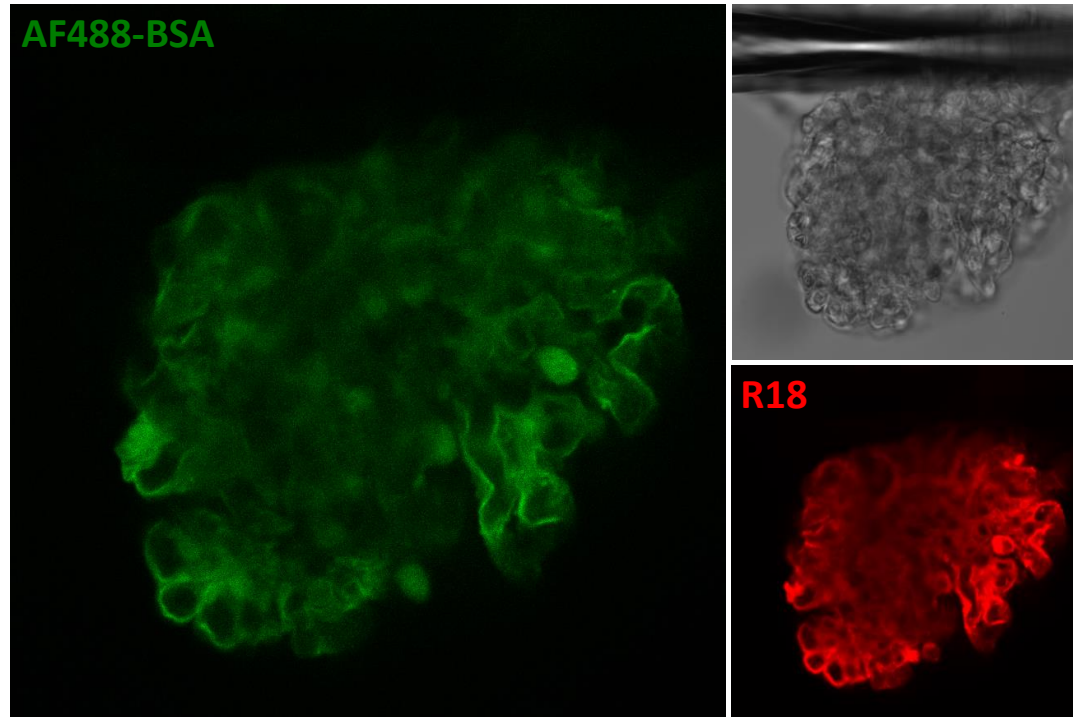
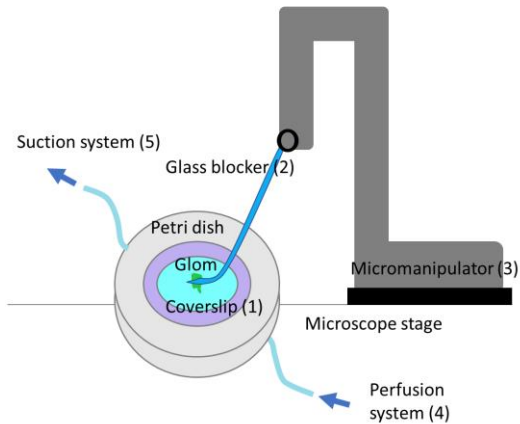
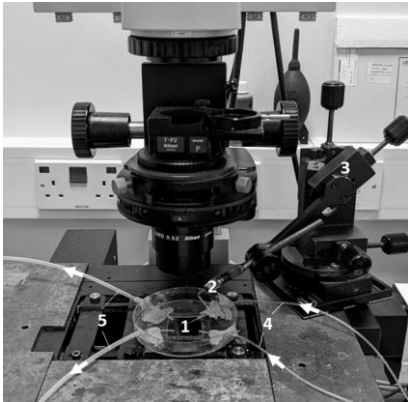


male Sprague
Dawley (150-200g)

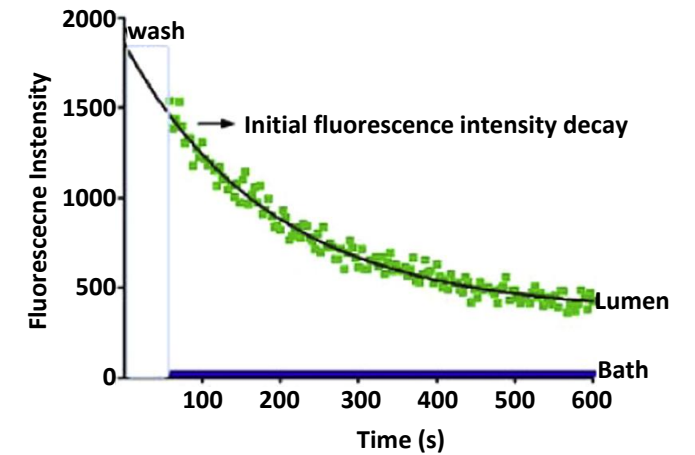
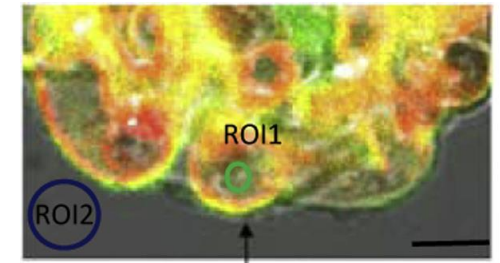


- Glomerular permeability assay
- Fixed glomeruli for staining

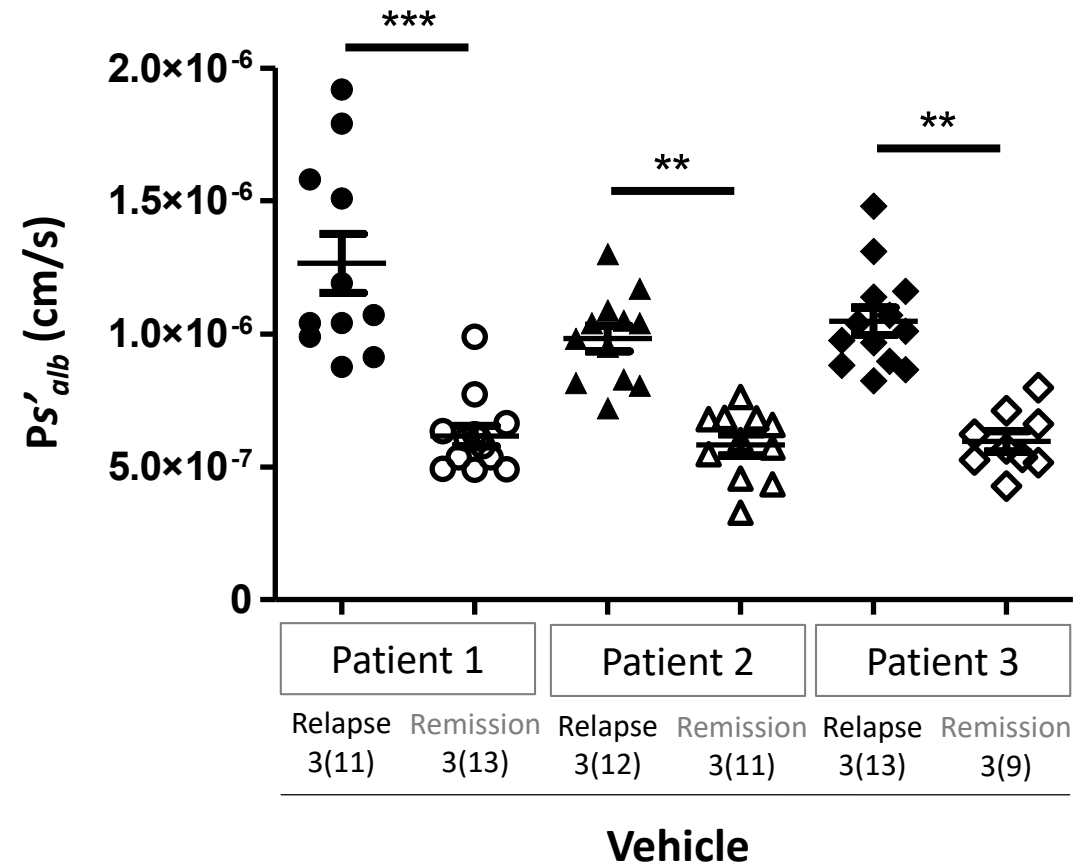
Our validated glomerular permeability assay directly measures the albumin permeability (Ps'_{alb}) of capillary loops within individually trapped glomeruli



Decline in fluorescence intensity of labelled albumin (ROI1) over time

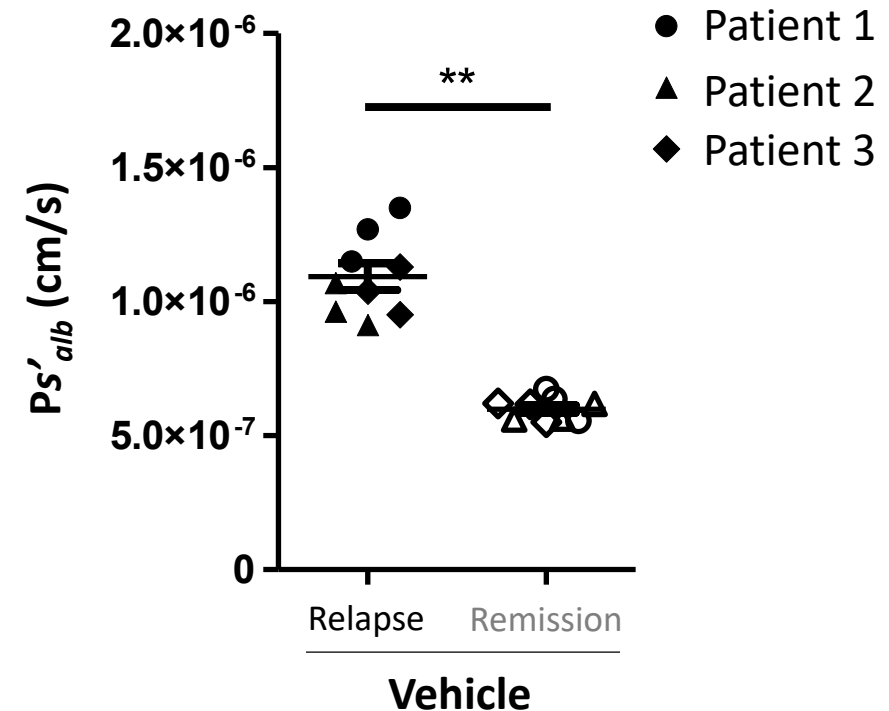
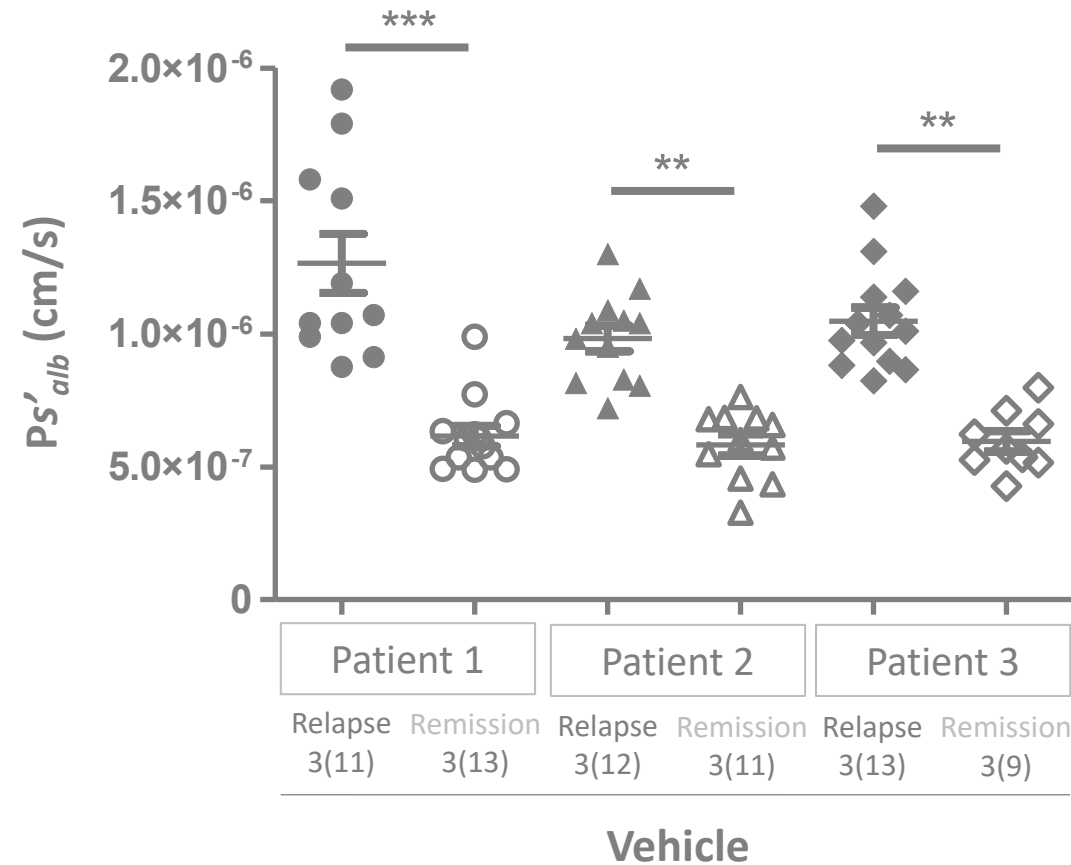


Human NS plasma increased glomerular albumin permeability in rat glomeruli



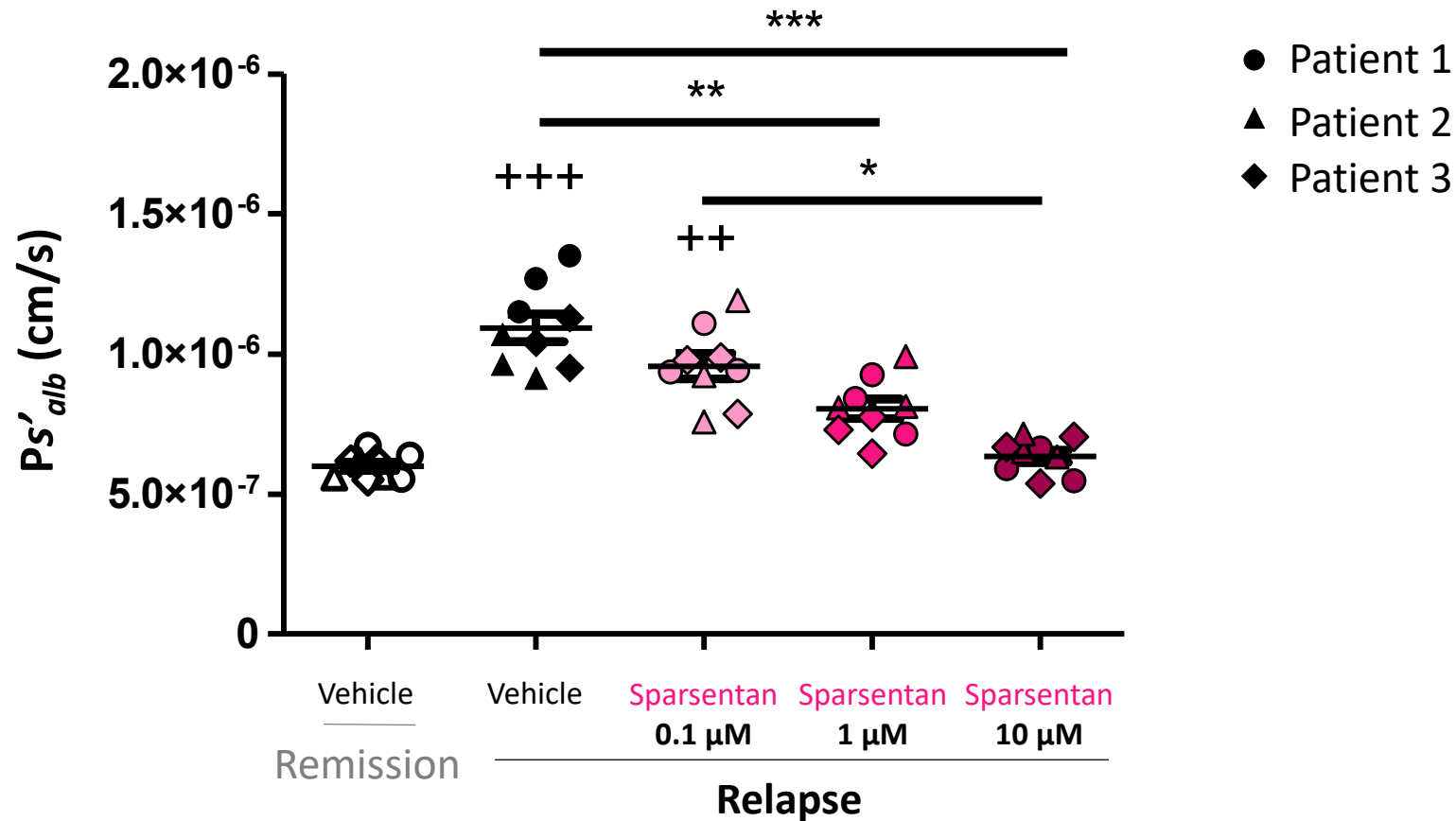
Ps'_{alb} , albumin permeability. # of animals (# of glomeruli). Mean \pm SEM; **, $p < 0.01$; ***, $p < 0.001$

Human NS plasma increased glomerular albumin permeability in rat glomeruli



Ps'_{alb} , albumin permeability. # of animals (# of glomeruli). Mean ± SEM; **, $p < 0.01$; ***, $p < 0.001$

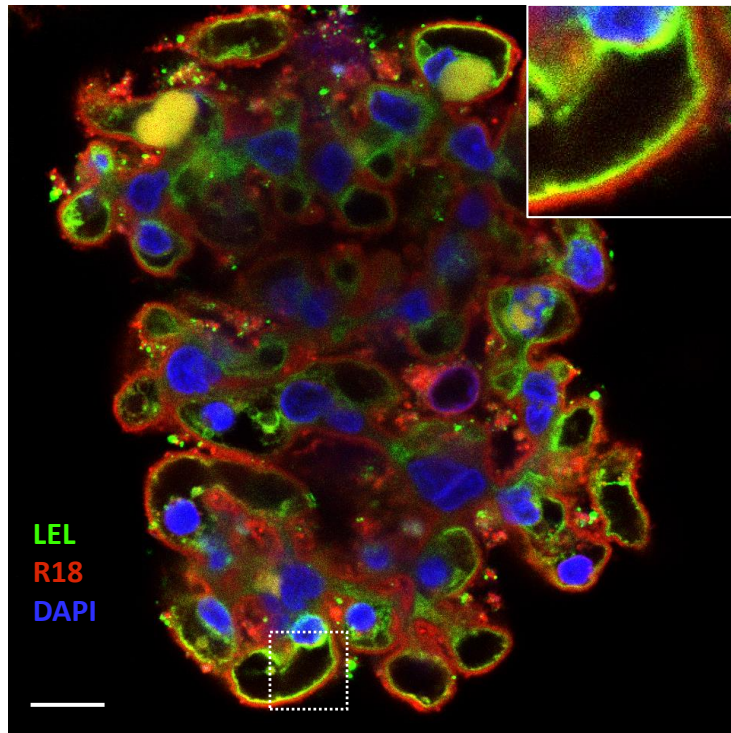
Sparsentan dose-dependently protected against increased glomerular albumin permeability resulting from human NS plasma



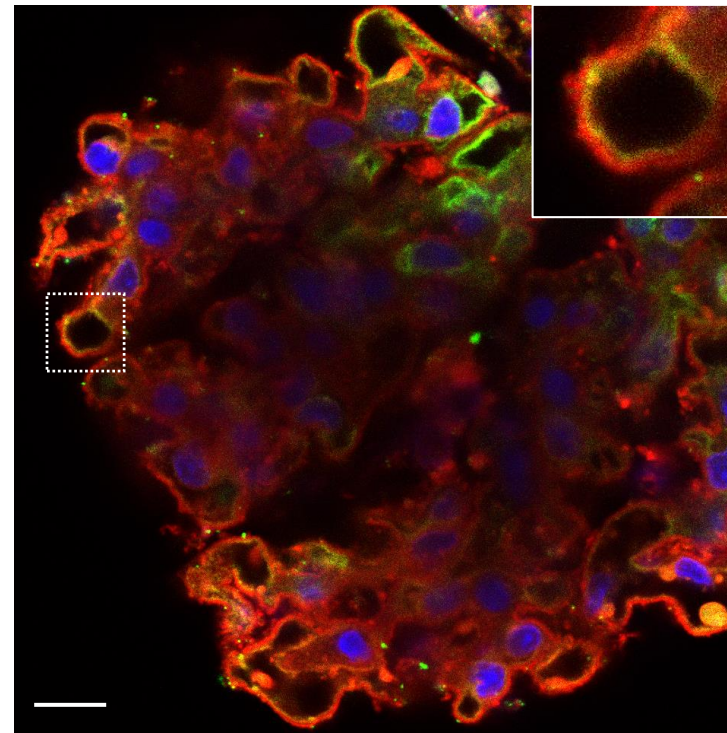
Mean \pm SEM; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. +, P -value vs. Remission+Vehicle

Sparsentan prevented eGlx damage in rat glomeruli exposed to human NS plasma

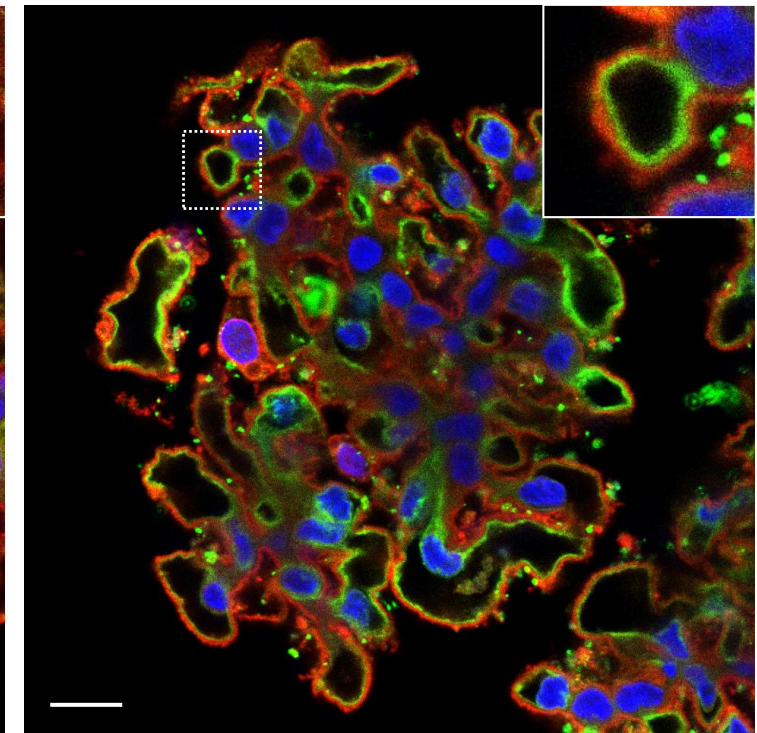
Remission + Vehicle



Relapse + Vehicle

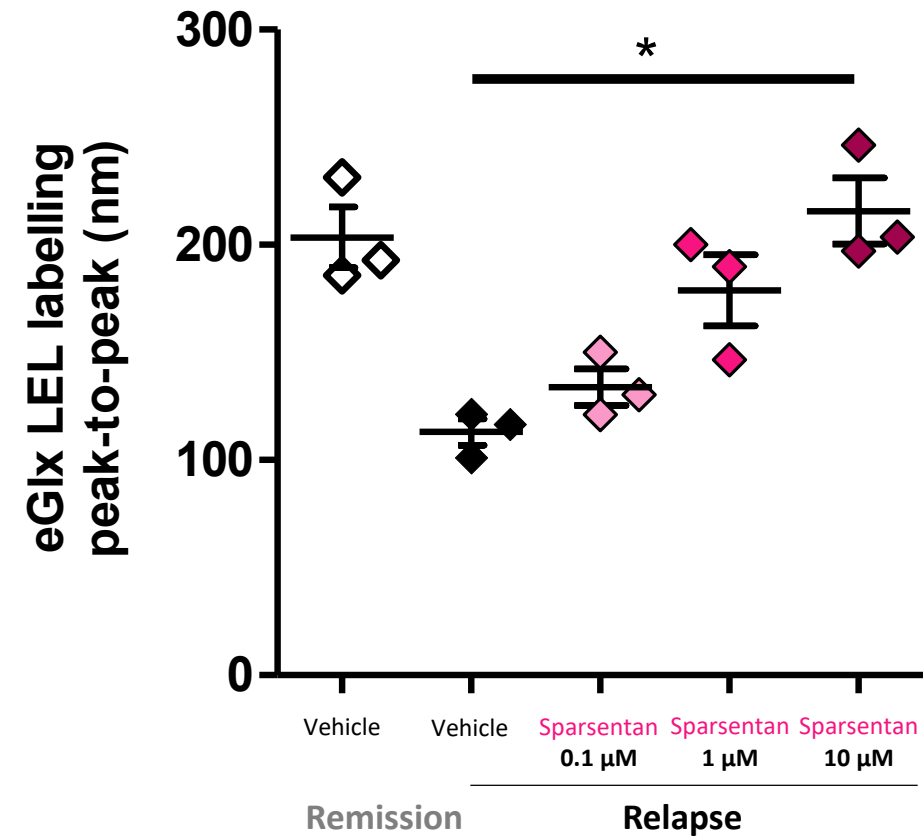
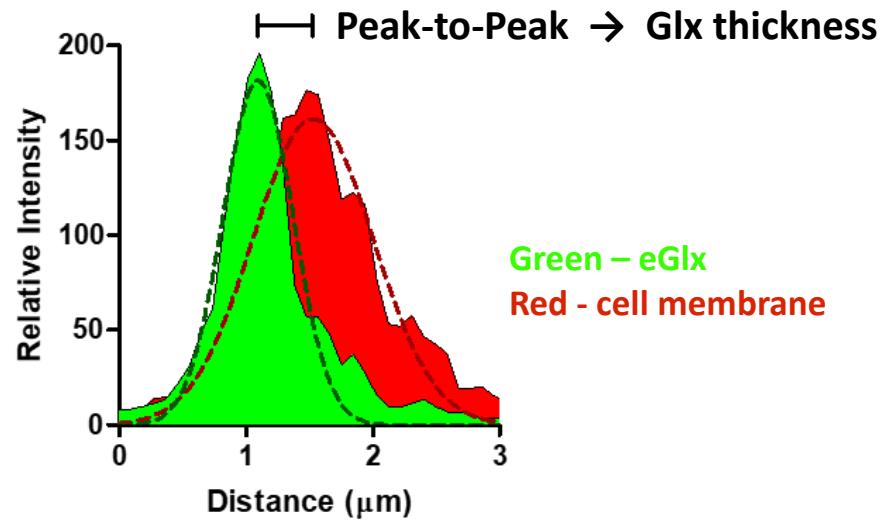
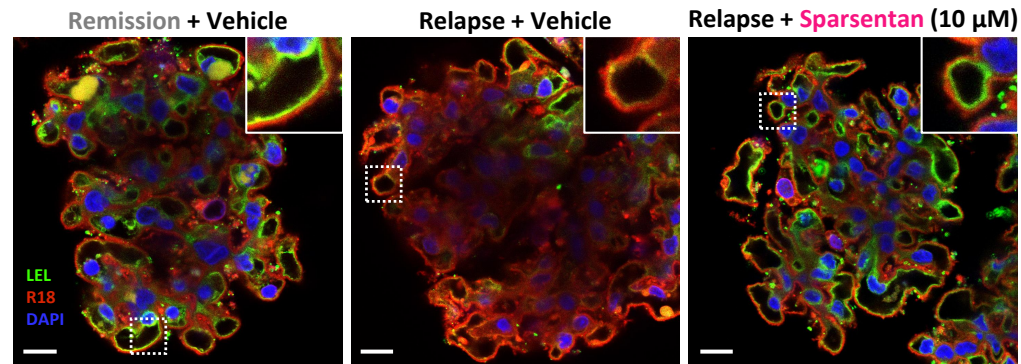


Relapse + Sparsentan (10 μ M)



LEL (*Lycopersicon esculentum* Lectin) - luminal glomerular eGlx
R18 (Octadecyl Rhodamine B Chloride) – cell membrane label
DAPI – nuclear label

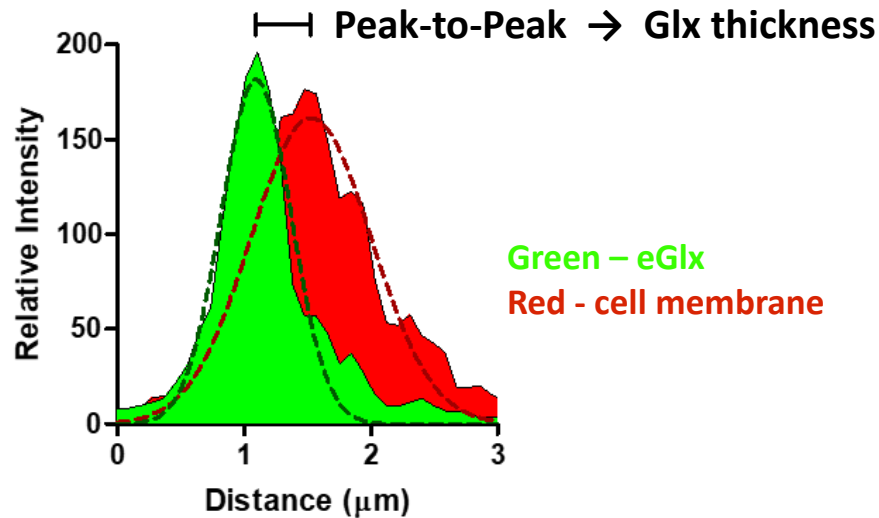
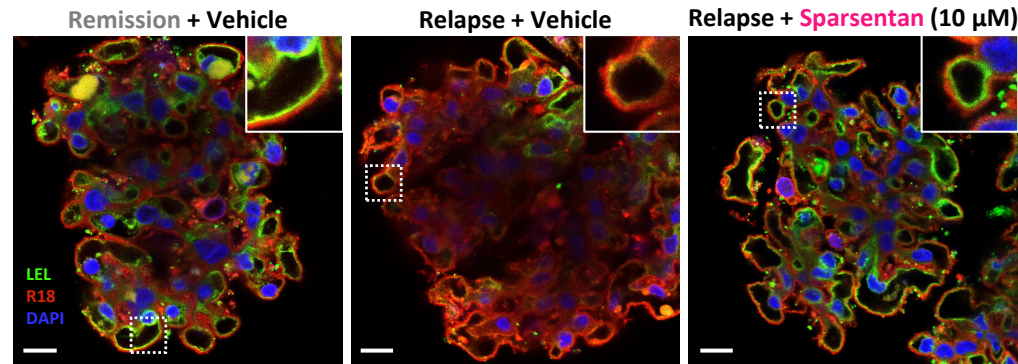
Sparsentan dose-dependently prevented eGlx damage in rat glomeruli exposed to human NS plasma



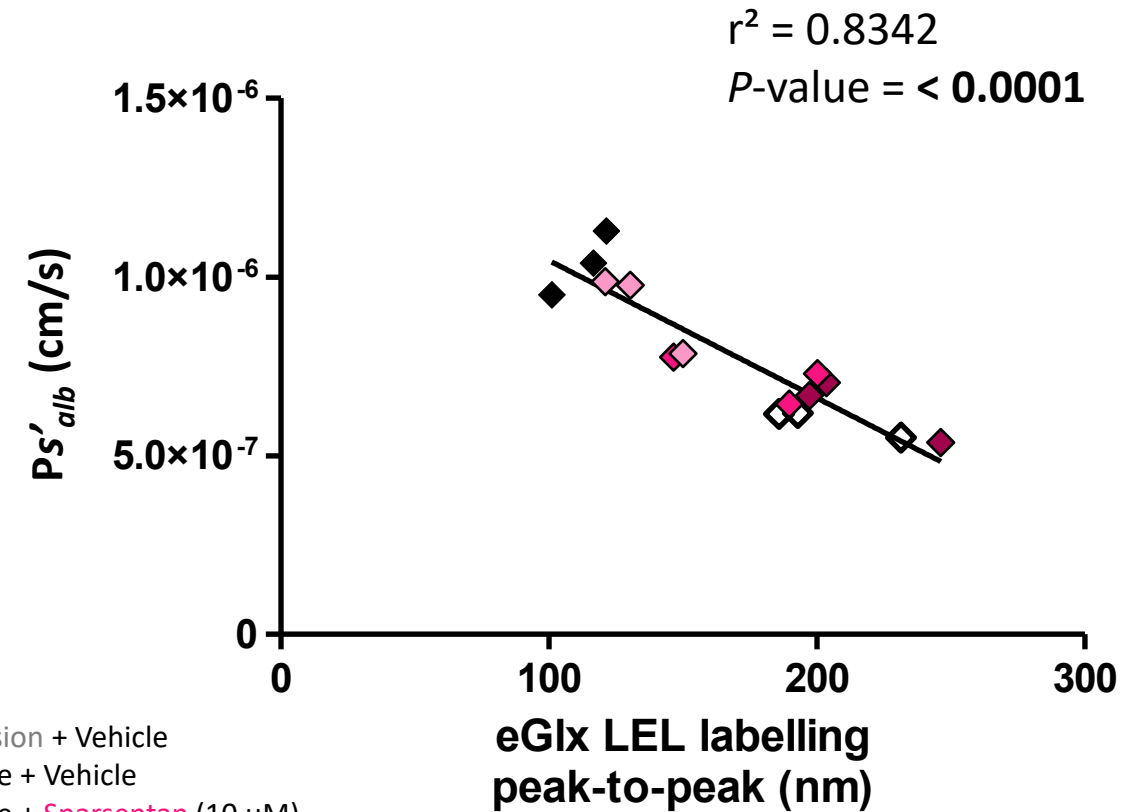
Mean ± SEM; *, $p < 0.05$

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The effect of sparsentan in preventing the NS-induced increase in glomerular permeability is correlated with protection from eGlx loss



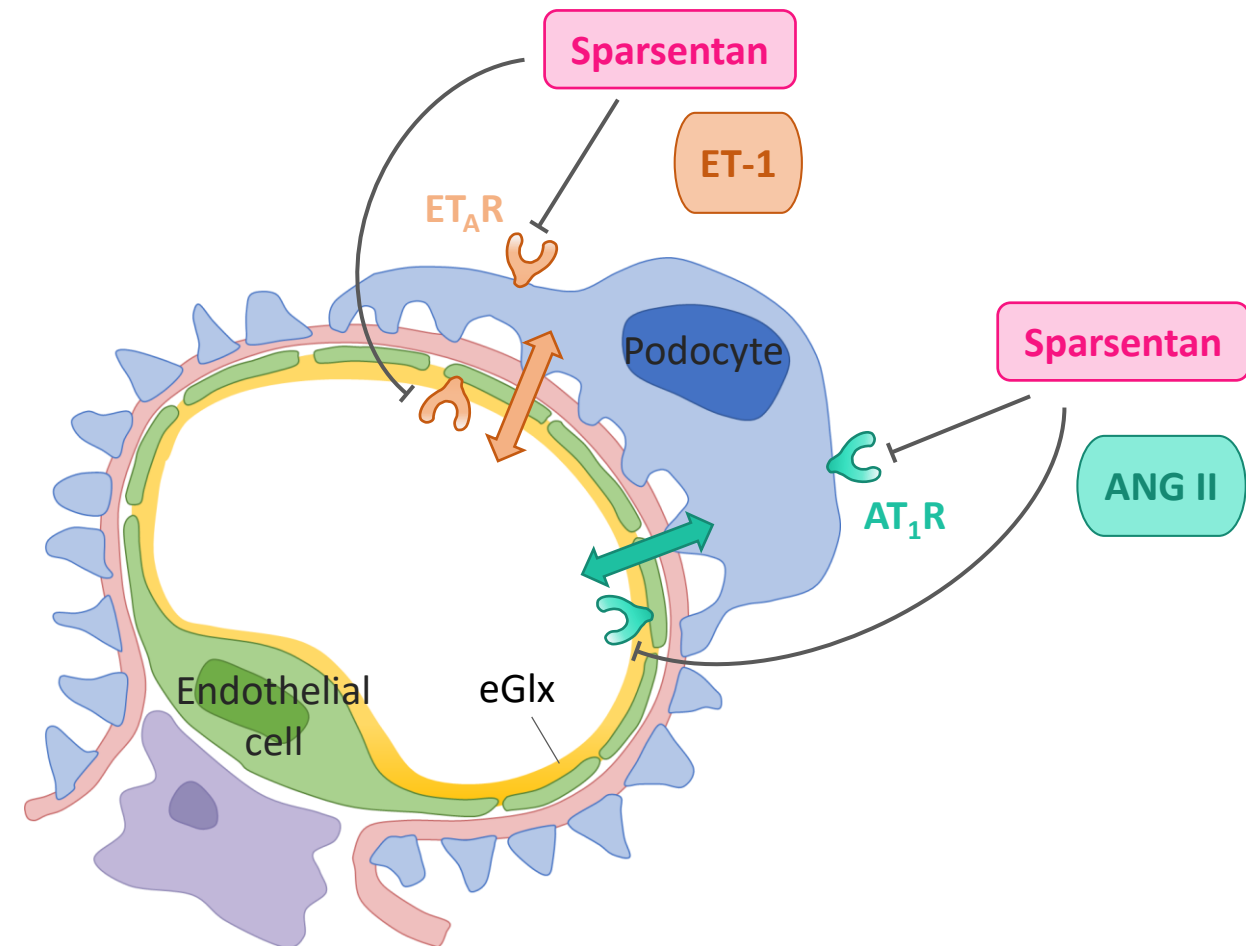
- ◇ Remission + Vehicle
- ◆ Relapse + Vehicle
- ◆ Relapse + Sparsentan (10 μM)
- ◆ Relapse + Sparsentan (1 μM)
- ◇ Relapse + Sparsentan (0.1 μM)



Sparsentan preserved glomerular eGlx and protected glomeruli from increased permeability following exposure to human NS plasma

SUMMARY

- Dual antagonism of ET_AR and AT₁R, with sparsentan, preserved the glomerular eGlx resulting in normalised glomerular permeability following incubation with NS plasma
- The direct action of sparsentan on the GFB could help maintain barrier integrity in NS, via glycocalyx protection



Acknowledgements



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Elizabeth Colby
Moin A. Saleem
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Simon C. Satchell

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