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Sparsentan, the dual endothelin angiotensin receptor antagonist (DEARA), attenuates albuminuria and protects from the development of renal injury to a greater extent than losartan in the gddY mouse model of IgA nephropathy; a 16-week study

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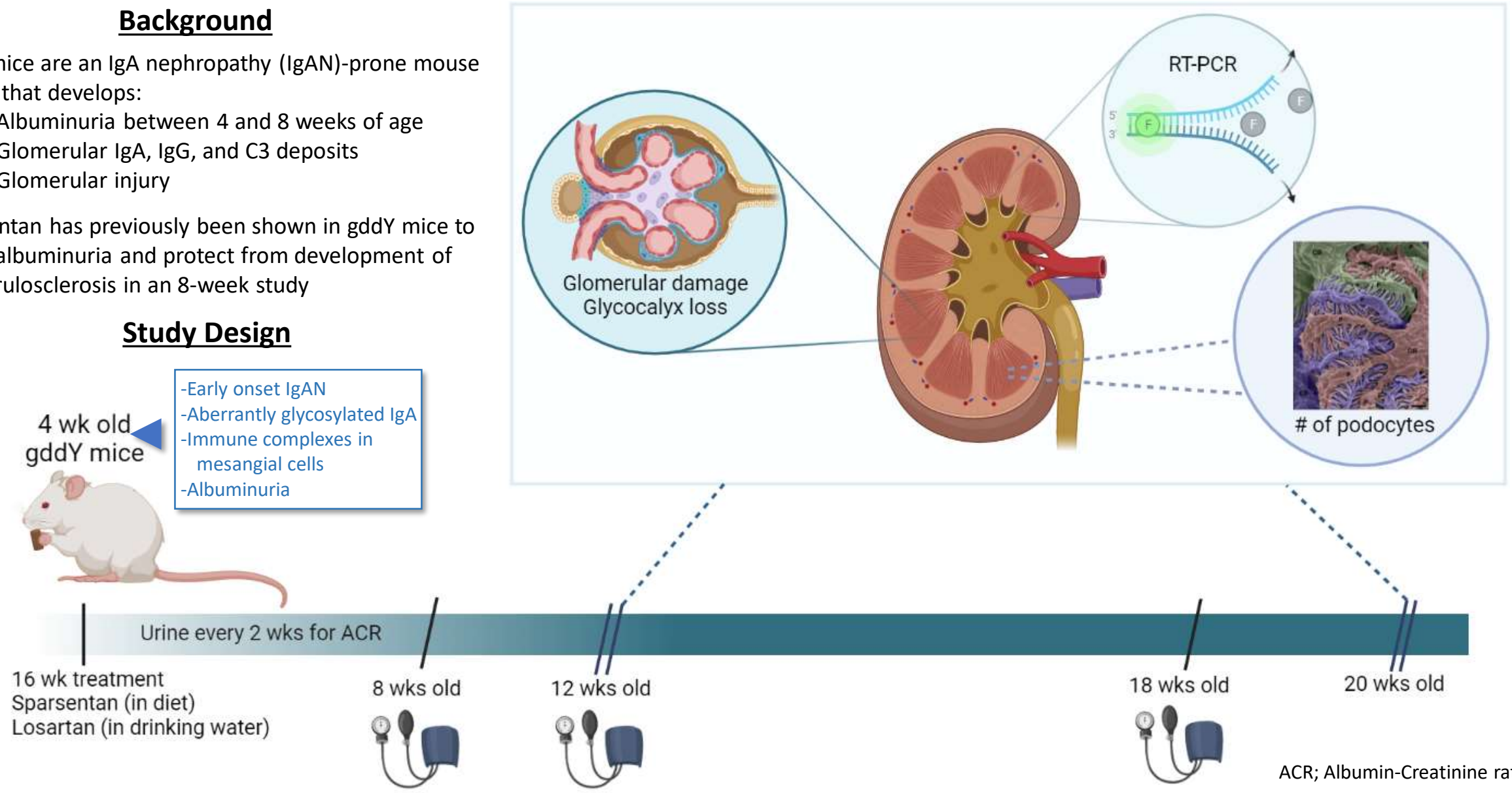
Study aim: Comparison of sparsentan (DEARA) and losartan (ARB) in gddY mice over 16 weeks of treatment

Background

- gddY mice are an IgA nephropathy (IgAN)-prone mouse model that develops:
  - Albuminuria between 4 and 8 weeks of age
  - Glomerular IgA, IgG, and C3 deposits
  - Glomerular injury
- Sparsentan has previously been shown in gddY mice to lower albuminuria and protect from development of glomerulosclerosis in an 8-week study

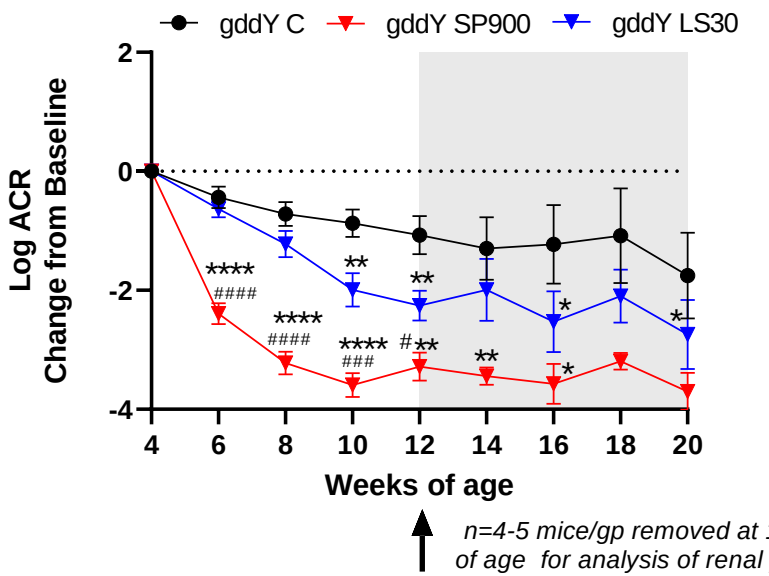
Study Design



ACR; Albumin-Creatinine ratio

Sparsentan lowers ACR more rapidly than losartan despite equivalent blood pressure effects

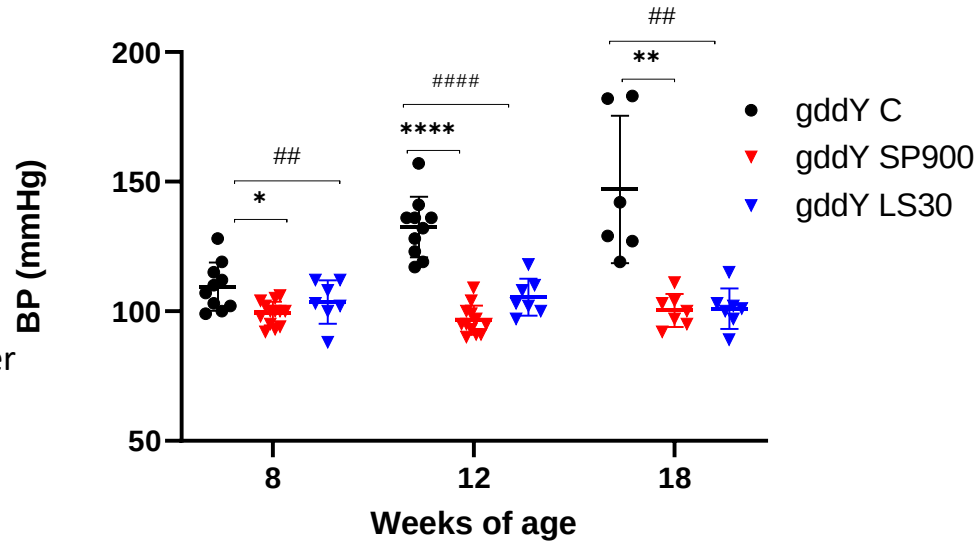
Log ACR Change From Baseline



C = control
LS30 = losartan 30 mg/kg drinking water
SP900 = sparsentan 900 ppm in diet

n=4-5 mice/gp removed at 12 weeks of age for analysis of renal pathology

Blood Pressure

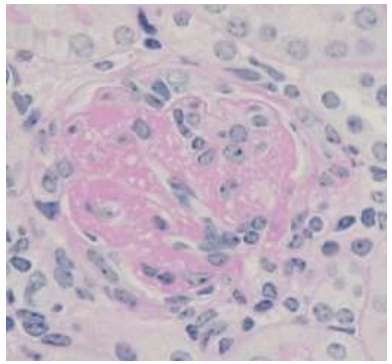
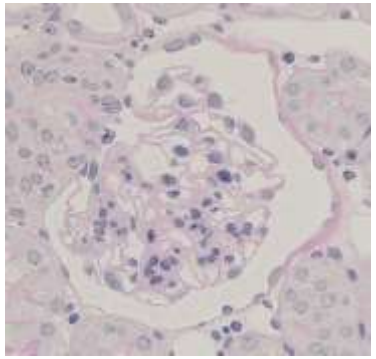
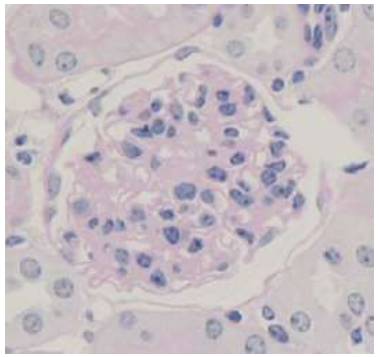
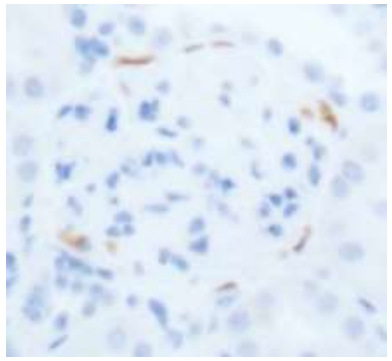
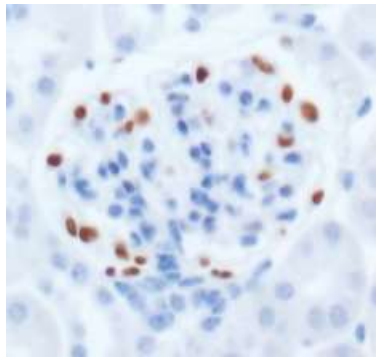
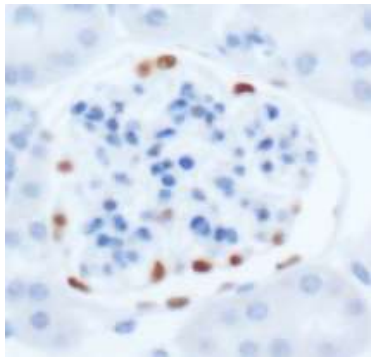
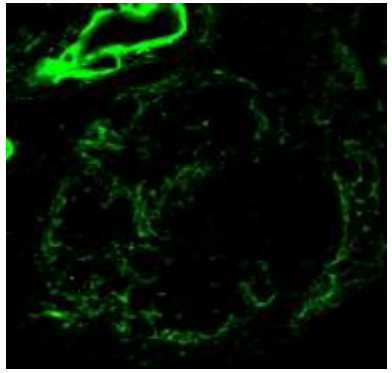
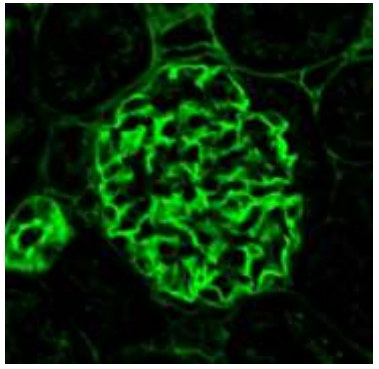
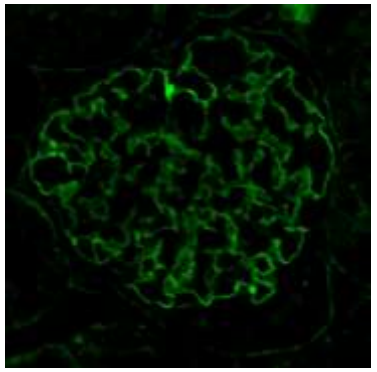


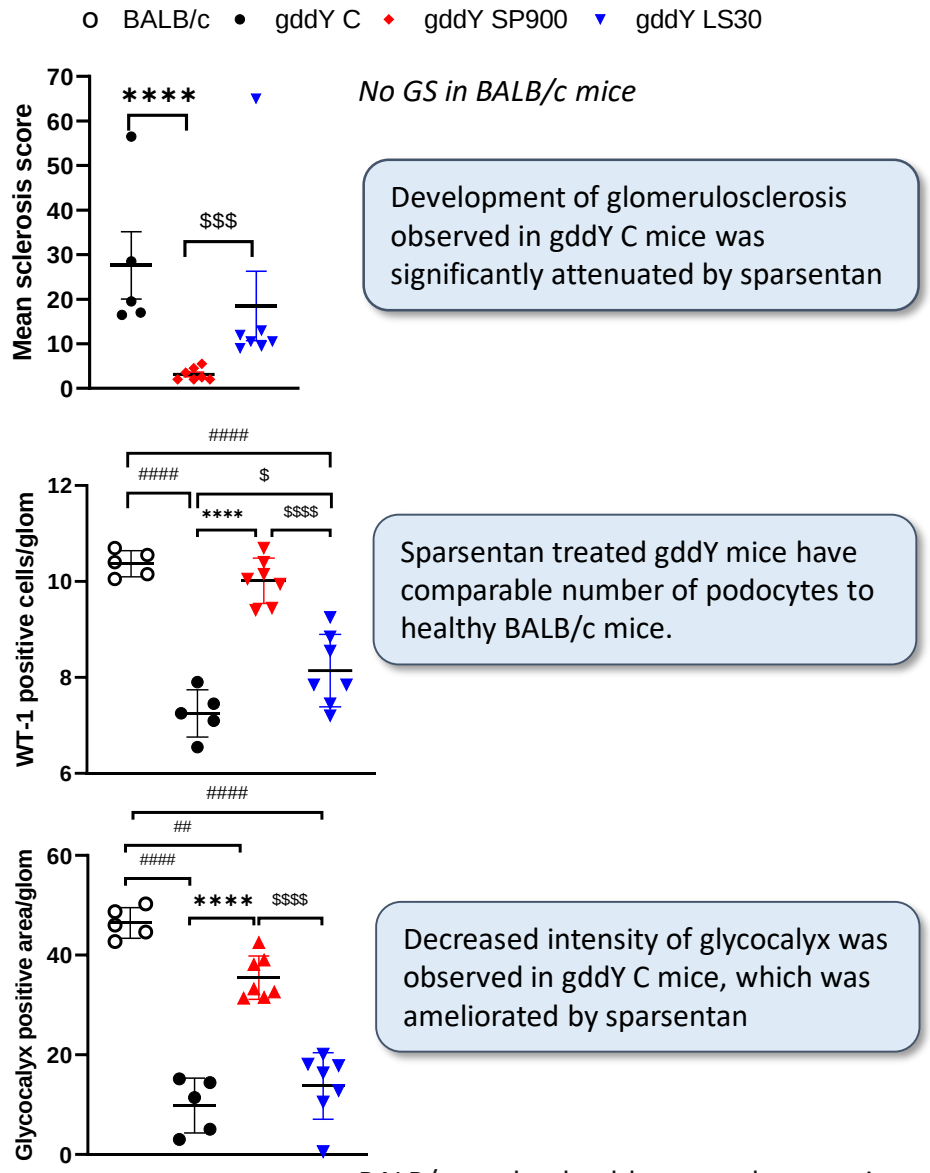
- Sparsentan produces a more rapid reduction in ACR from initiation of treatment compared to losartan in gddY mice
- Reduction in ACR from baseline in sparsentan-treated mice is significantly greater compared to losartan treatment during the first 8 weeks of treatment
- Sparsentan and losartan significantly lower BP similarly compared to gddY control mice

Log ACR: P-value from Mixed-Effect Model Repeated Measure (MMR).
****P<0.0001, **P<0.01, *P<0.05 compared to gddY C;
####P<0.0001, ###P<0.001, #P<0.05 gddY SP900 compared to LS30.
gddY C n=10 (4-12 weeks of age), n=4 (12-20 weeks of age),
gddY SP90 and LS30 n=12 (4-12 weeks of age), n=7 (12-20 weeks of age).

Blood Pressure: *P<0.05, **P<0.01, ****P<0.0001 gddY SP900 vs gddY C;
##P<0.01, ####P<0.0001 gddY LS30 vs gddY C.
Weeks of age 8 and 12 one-way ANOVA; age 18 Kruskal-Wallis test.

Sparsentan delays progression of glomerulosclerosis, podocyte loss, and glycocalyx damage to a significantly greater extent than losartan after 16 weeks of treatment

	gddY C	gddY SP900	gddY LS30
Glomerulosclerosis			
Podocyte Number (WT-1 staining)			
Glycocalyx (FITC-labelled lectin)			



Development of glomerulosclerosis observed in gddY C mice was significantly attenuated by sparsentan

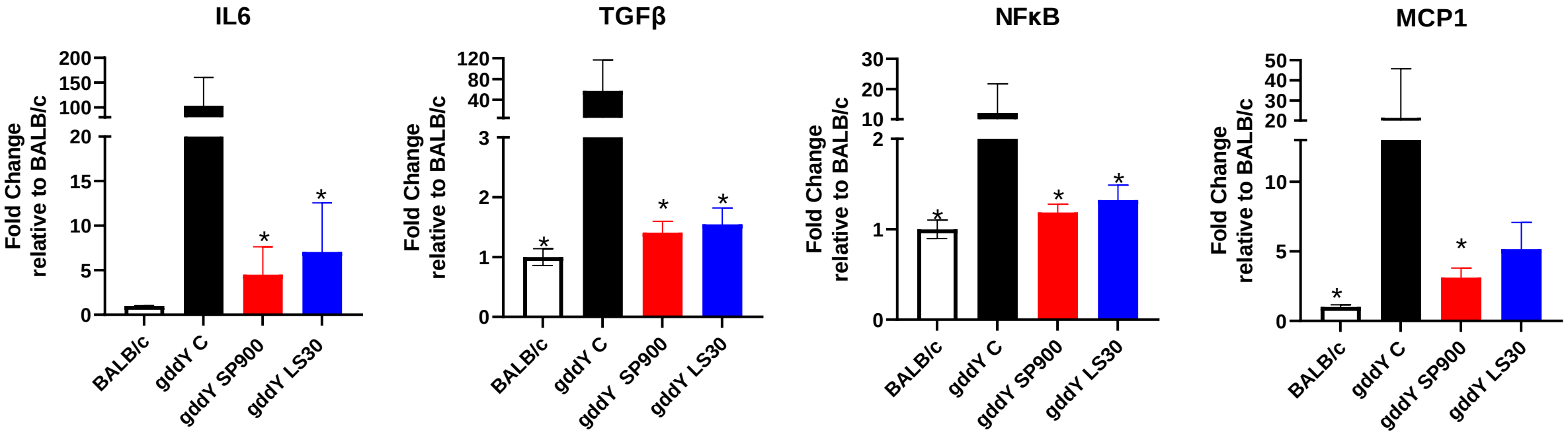
Sparsentan treated gddY mice have comparable number of podocytes to healthy BALB/c mice.

Decreased intensity of glycocalyx was observed in gddY C mice, which was ameliorated by sparsentan

****P<0.0001; **P<0.01 gddY C vs SP900 ; ####P<0.0001 vs. BALB/c; $P<0.05, $$$P<0.001, $$$$P<0.0001 vs LS30 following one-way ANOVA.

BALB/c used as healthy control comparison

Sparsentan and losartan prevent the increase in expression of immune and pro-inflammatory signaling in kidneys of gddY mice



Summary of Attenuation of Immune-related Gene Changes Relative to gddY Mice

Treatment	IL-6	TGFβ	NFκβ	MCP-1
Sparsentan 900 ppm	↓*	↓*	↓*	↓*
Losartan 30 mg/kg	↓*	↓*	↓*	↓

8 weeks treatment
4-12 weeks of age

Mann-Whitney test *P<0.05 vs gddY C; BALB/c n=5 (IL-6 n=2), gddY C n=4, gddY SP900 n=5; gddY LS30 n=5.

Summary

- Treatment of the gddY mouse model of IgA nephropathy with the DEARA sparsentan resulted in a more rapid attenuation of ACR and greater protection from glomerulosclerosis and glycocalyx damage than losartan, despite equivalent lowering of blood pressure
- Sparsentan protected the glomeruli from loss of podocytes in gddY mice
- Both losartan and sparsentan prevented increases in inflammatory gene expression in 12-week-old mice
- These data suggest that the additional benefit of sparsentan over losartan is independent of blood pressure and anti-inflammatory mechanisms in the gddY mouse model and may be attributable to its dual mechanism of action
- These data, if translated to the clinic, support sparsentan as a possible new therapeutic approach to IgA nephropathy

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