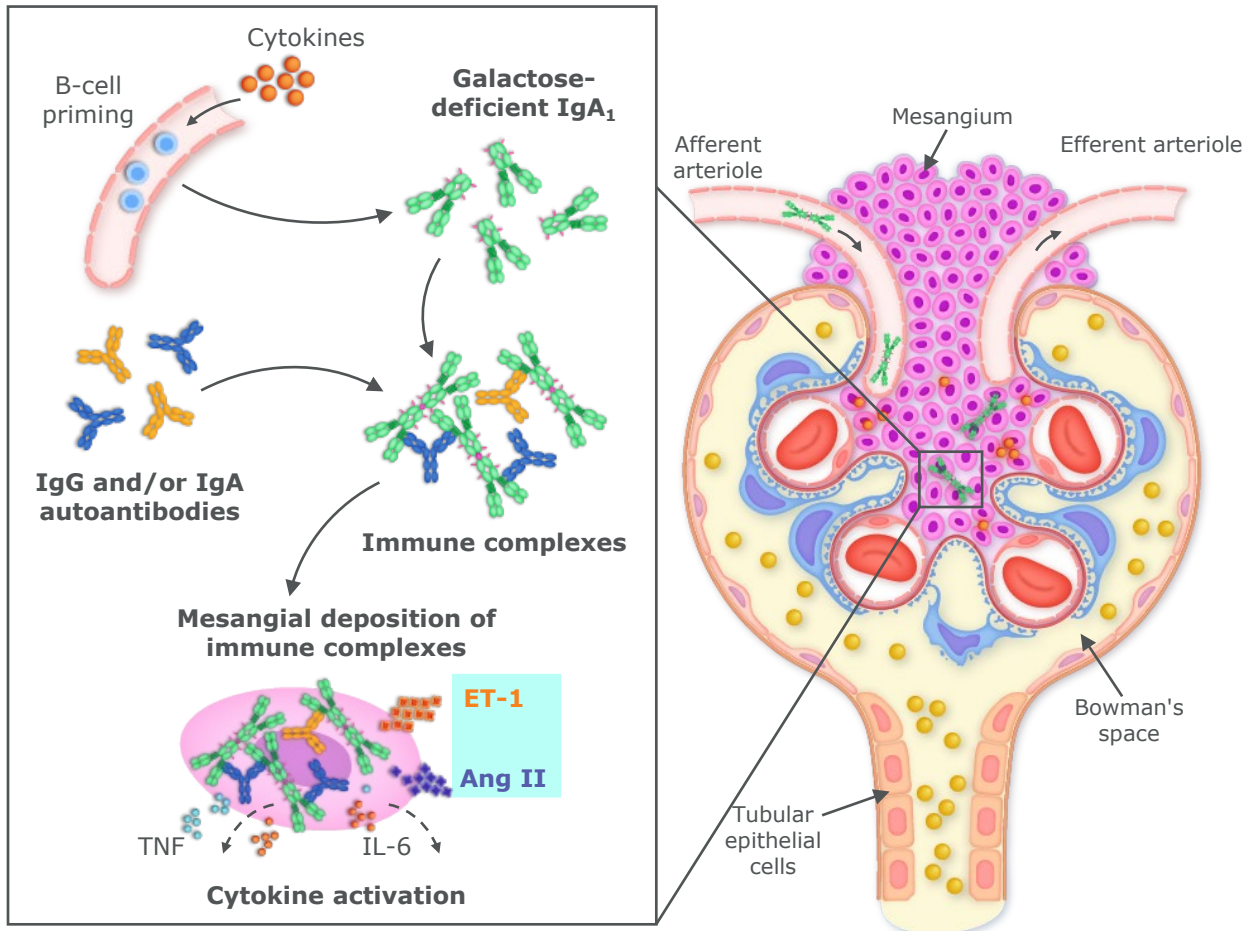
IgA Nephropathy Disease Pathophysiology: Focus on Endothelin-1 and Angiotensin II

MA-SP-23-0077

Multiple Factors Are Involved in the Pathogenesis of IgA Nephropathy: Multi-Hit Model



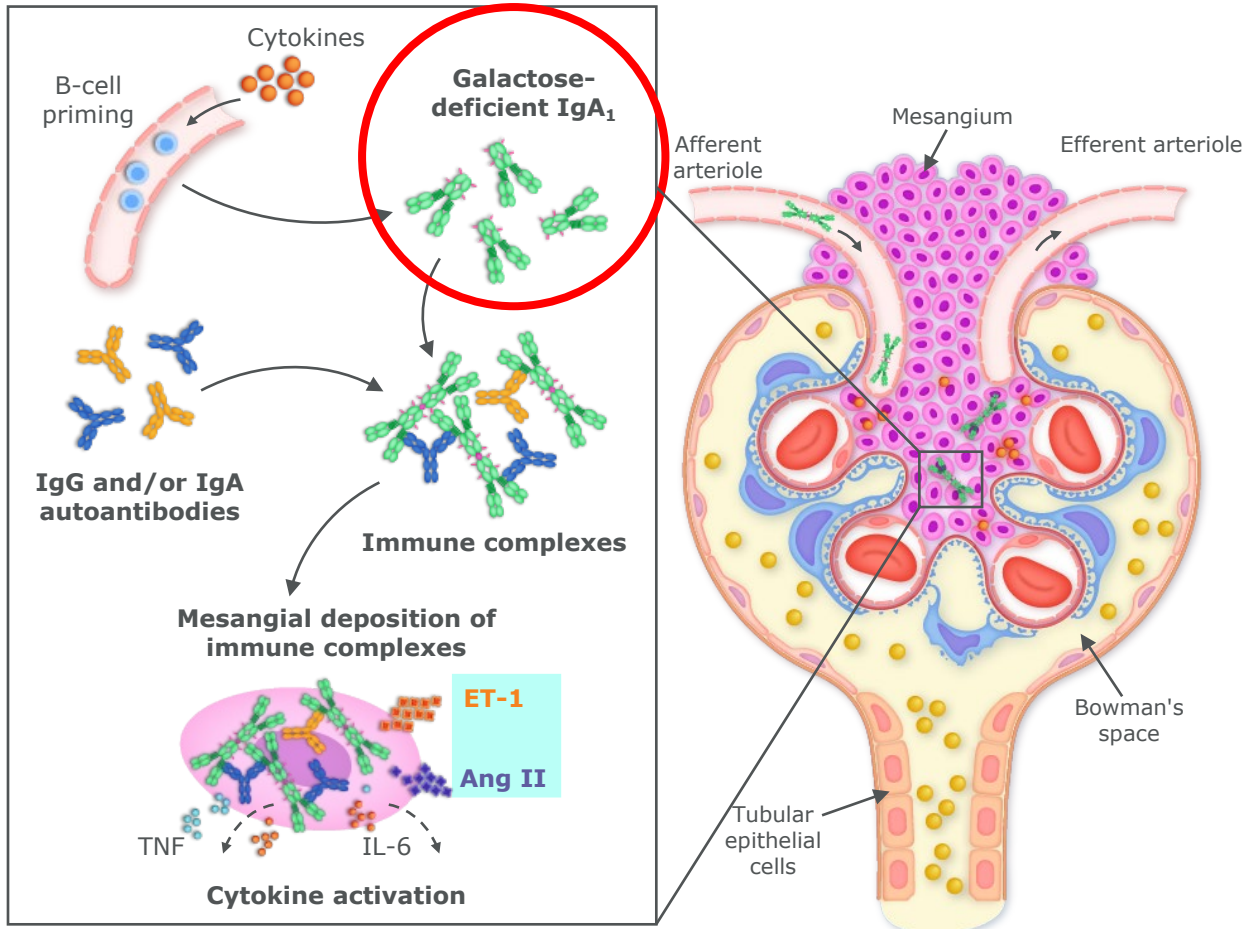
Many factors may influence susceptibility to the development and pathogenesis of IgA nephropathy, including genetic factors,[1–5] environmental factors,[1,2,5] and lifestyle factors[1,3–5]

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; 2. Maiguma M, *et al. PLoS One* 2014; 9:e90558; 3. Coppo R. *Nephrol Dial Transplant* 2015; 30:360–366;
4. Yuzawa Y, *et al. Clin Exp Nephrol* 2016; 20:511–535; 5. Penfold RS, *et al. Int J Nephrol Renovasc Dis* 2018; 11:137–148. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748.

TRAVERE THERAPEUTICS

Multiple Factors Are Involved in the Pathogenesis of IgA Nephropathy: Multi-Hit Model



Patients with IgA nephropathy have underglycosylated IgA_1, resulting in increased levels of circulating galactose-deficient IgA_1[1–4]

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; 2. Knoppova B, *et al. Front Immunol* 2016; 7:1–20; 3. Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414;
4. Lai K, *et al. Nat Rev Dis Primers* 2016; 2:16001. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414;
Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904;
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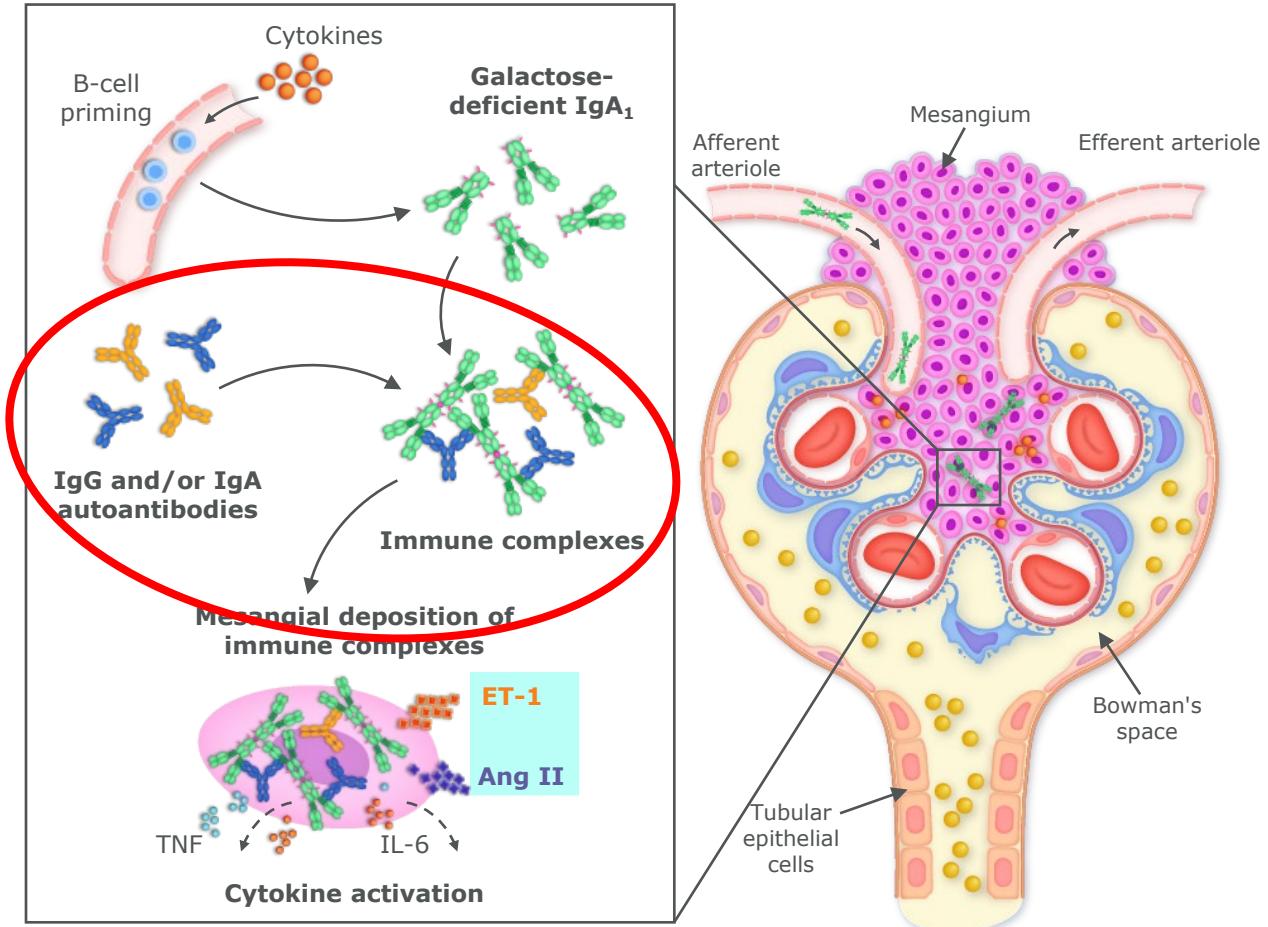

IgG and/or IgA isotype antibodies are synthesized; these antibodies recognize and bind to galactose-deficient IgA_1, forming immune complexes[1–4]

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; 2. Knoppova B, *et al. Front Immunol* 2016; 7:1–20; 3. Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414;
4. Lai K, *et al. Nat Rev Dis Primers* 2016; 2:16001. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414;
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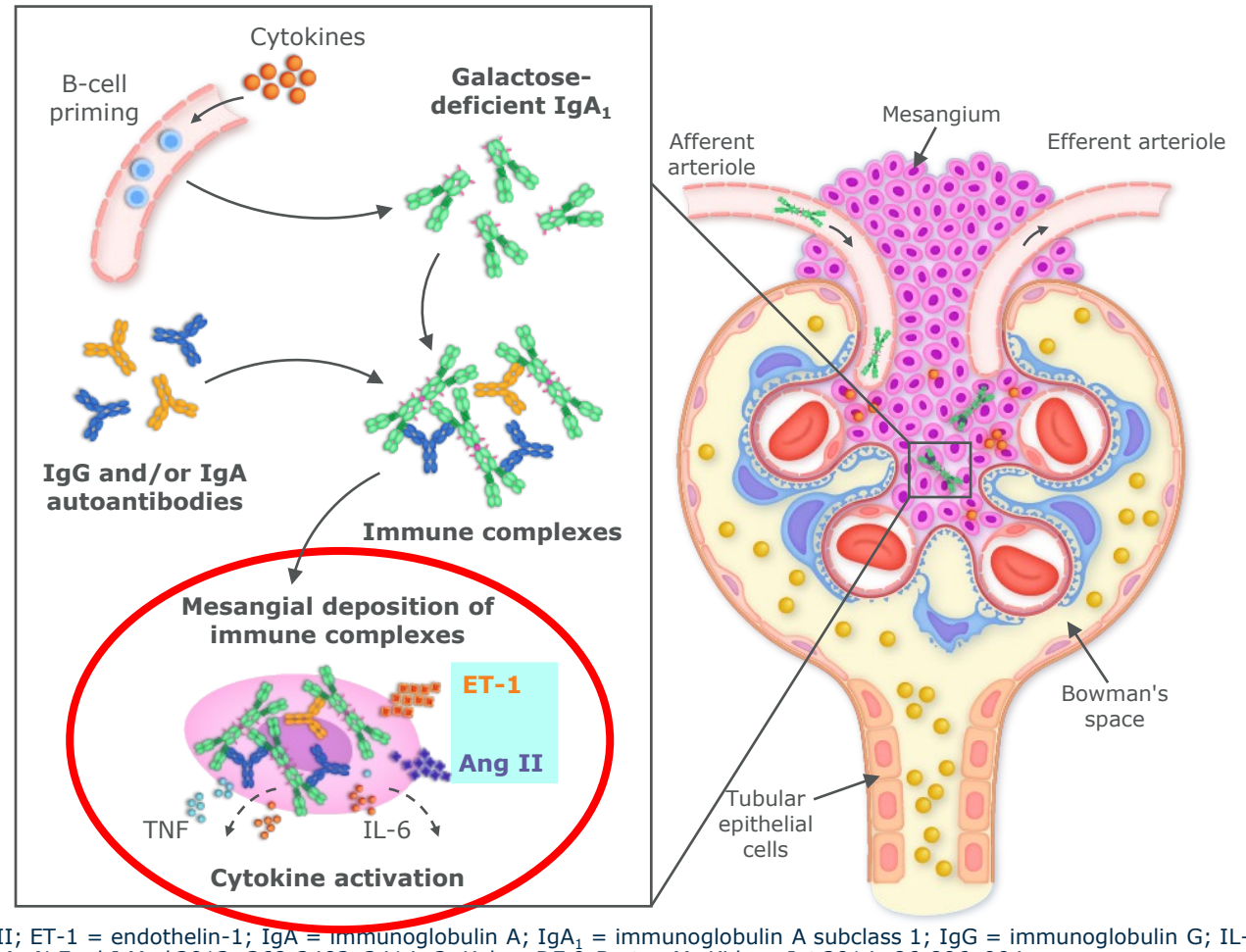
Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748.

TRAVERE THERAPEUTICS

ET-1 and Ang II Play a Key Role in the Pathophysiology of IgA Nephropathy



Immune complexes are deposited in the mesangium to cause glomerular injury by:[1,2]

- **Mesangial cell proliferation**
- **Pro-inflammatory** and **pro-fibrotic cytokine secretion**
- **Extracellular matrix production**
- Upregulation of growth factors, including **ET-1** and **Ang II**

Through cross-talk, **Ang II upregulates ET-1 production** and **ET-1 increases** the conversion of Ang I to **Ang II**[3]

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; 2. Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904;
3. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414;
Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904;
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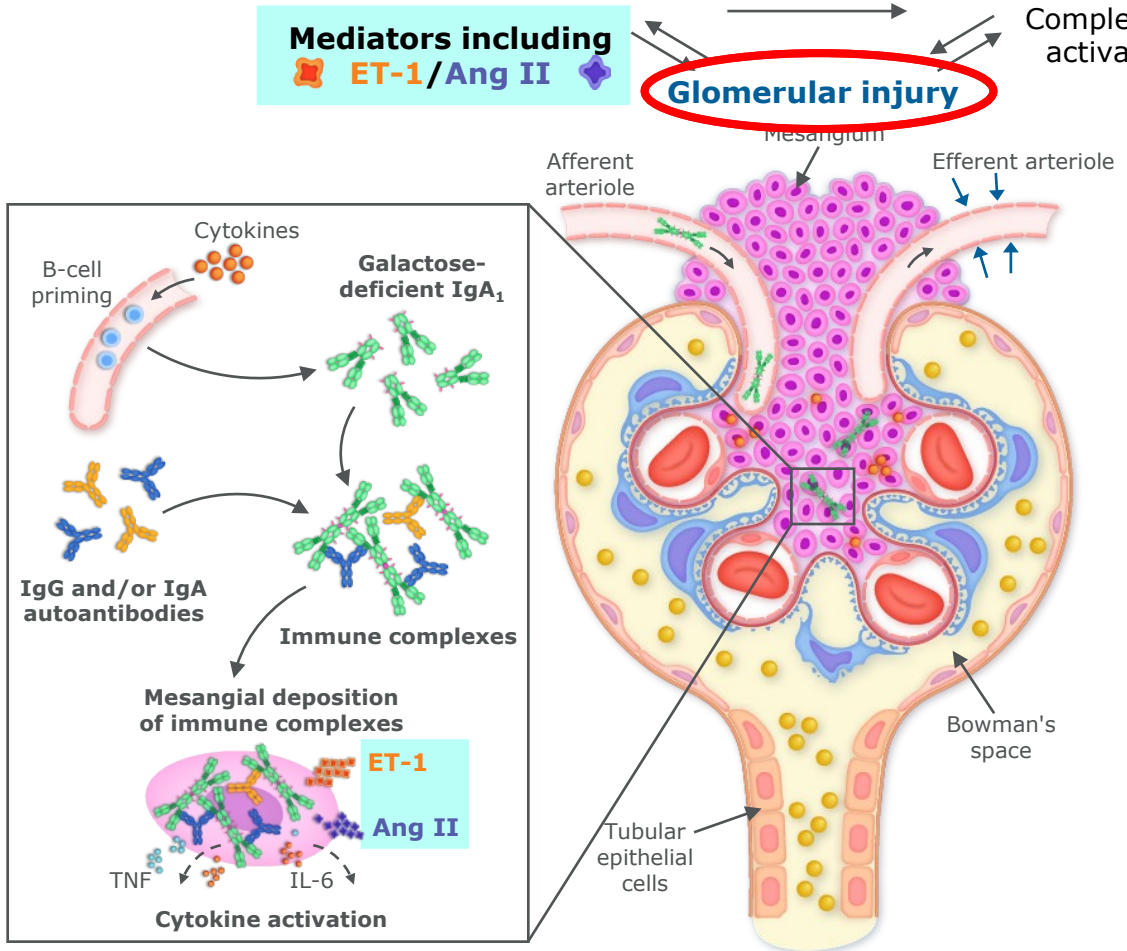

ET-1 and **Ang II** act in tandem via their receptors, **ET_AR and AT_1R**, to **amplify** glomerular injury via:[1,2]

- Mesangial cell proliferation
- Inflammation
- Extracellular matrix production
- Podocyte injury and apoptosis
- Detrimental changes in glomerular hemodynamics

Ang II = angiotensin II; AT_1R = angiotensin II subtype 1 receptor; ET-1 = endothelin-1; ET_AR = endothelin-1 type A receptor; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor. 1. Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; 2. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884.
Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748.

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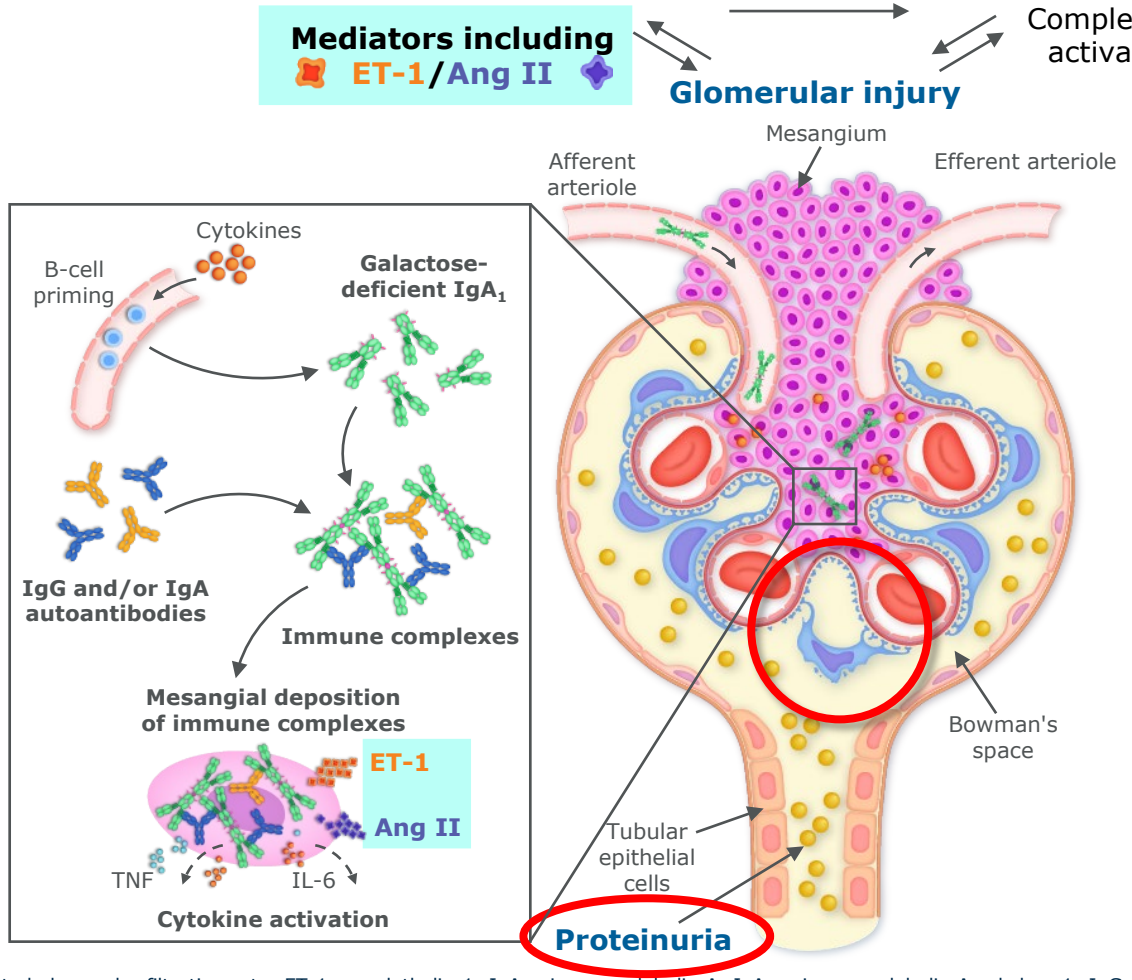


As a result of glomerular injury, the **glomerular filtration barrier is compromised**, leading to **proteinuria**, **hematuria**, and **glomerulosclerosis**[1–3]

Proteinuria further **increases ET-1** and **Ang II** levels[2,5]

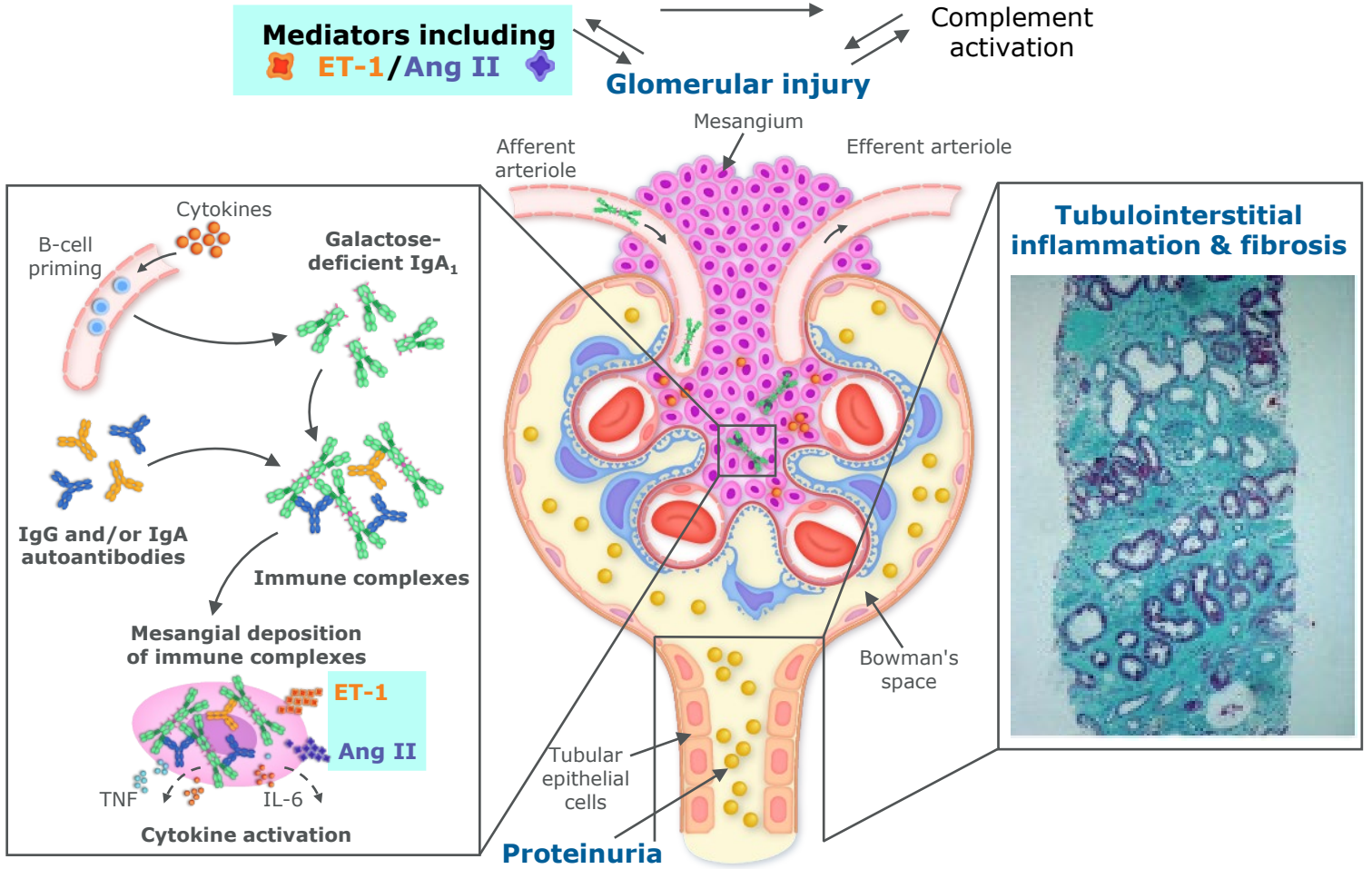
Elevated proteinuria over time is associated with **reduction in eGFR** and greater risk of **progression** in IgA nephropathy[4]

Ang II = angiotensin II; eGFR = estimated glomerular filtration rate; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; 2. Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; 3. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; 4. Pitcher D, *et al. Clin J Am Soc Nephrol* 2023; doi: 10.2215/CJN.0000000000000135; 5. Mezzano SA, *et al. Hypertension* 2001; 38:635–638. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748.

TRAVERE THERAPEUTICS

Proteinuria Drives Further Injury in the Tubulointerstitial Compartment



After entering the urinary space, leaked proteins and IgA_1-containing immune complexes **drive tubular atrophy and interstitial fibrosis**[1]

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748. Tubulointerstitial inflammation & fibrosis image from: Cao Y, *et al. Dis Markers* 2019; 2019:2424751.

TRAVERE THERAPEUTICS

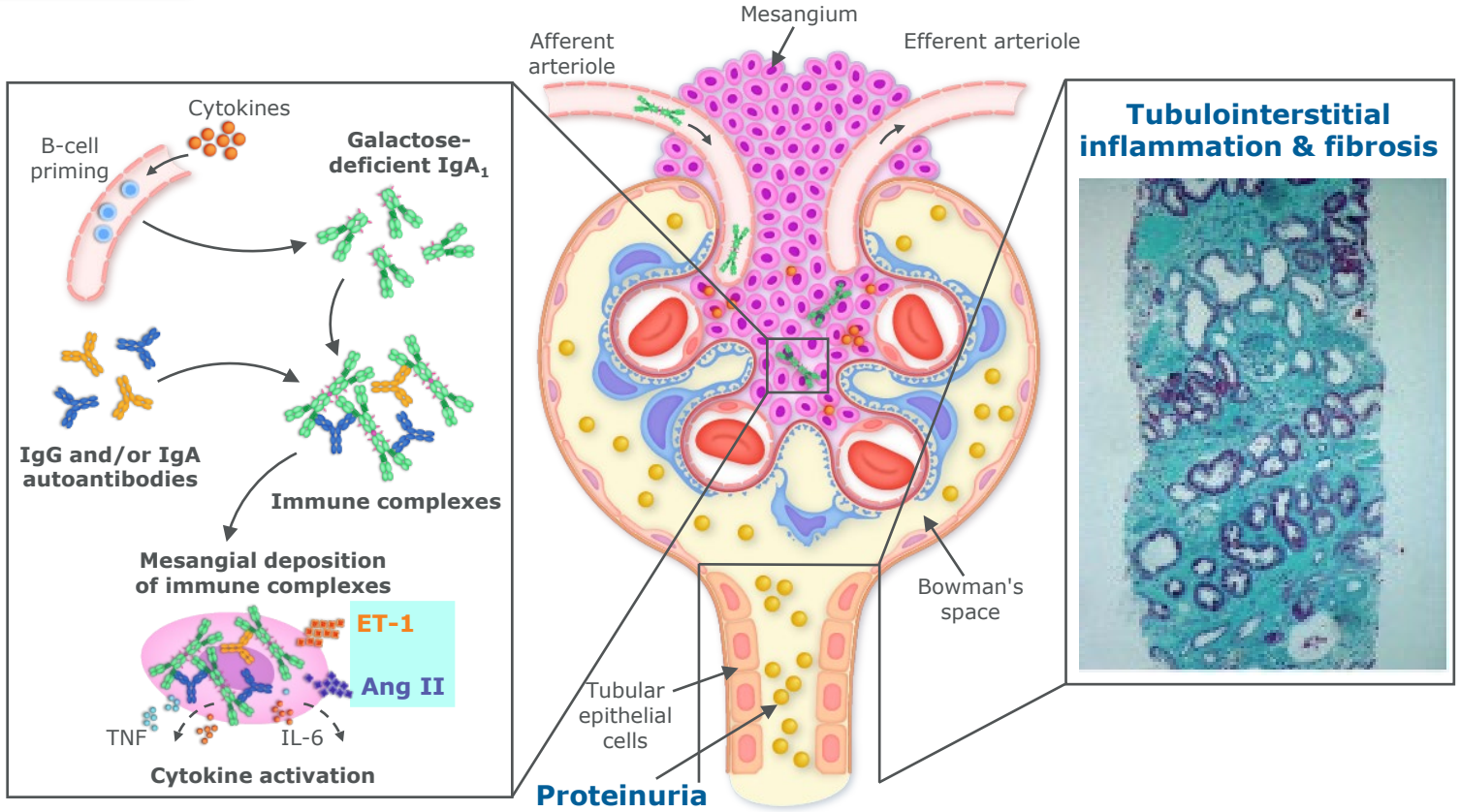
Sparsentan* Is a Dual Endothelin Angiotensin Receptor Antagonist, or DEARA

Sparsentan blocks the actions of ET-1 and Ang II[1]

Mediators including ET-1/Ang II

Glomerular injury

Complement activation



Tubulointerstitial inflammation & fibrosis

* Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression.

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

1. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748. Tubulointerstitial inflammation & fibrosis image from: Cao Y, *et al. Dis Markers* 2019; 2019:2424751.

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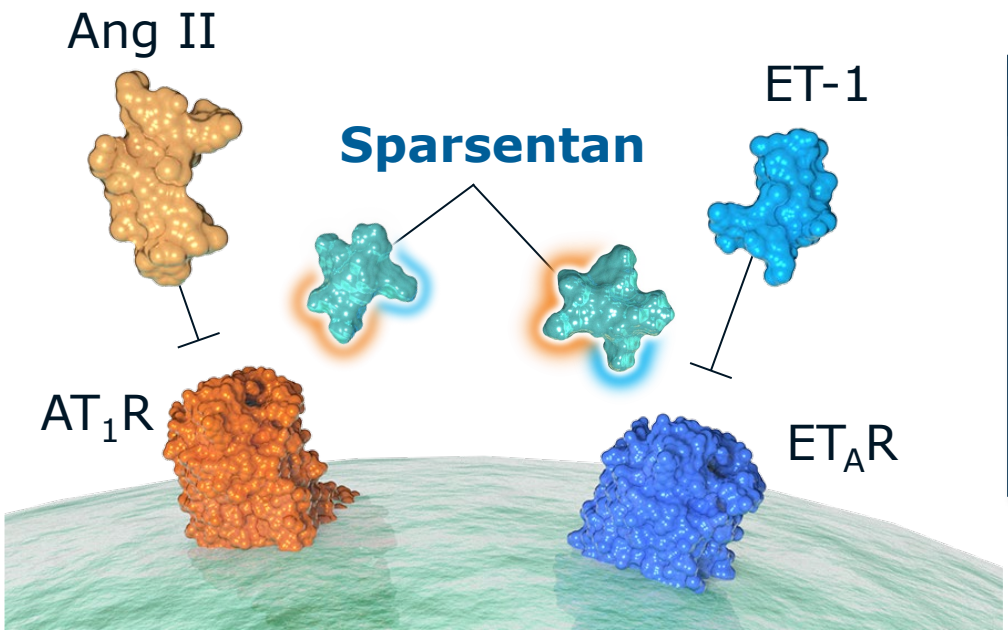
Sparsentan Is a Dual Endothelin Angiotensin Receptor Antagonist, or DEARA

Sparsentan blocks
of ET-1 and

Complement

Sparsentan is a non-immunosuppressive, highly selective dual antagonist of both endothelin-1 type A receptors (ET_AR) and angiotensin II subtype 1 receptors (AT_1R)[1–3]



Sparsentan is:[1–3]

- A single molecule
- A dual **ET_AR** and **AT_1R** antagonist
- An oral tablet

* Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression.
Ang II = angiotensin II; AT_1R = angiotensin II subtype 1 receptor; ET-1 = endothelin-1; ET_AR = endothelin-1 type A receptor.
1. Kowala MC, *et al. J Pharmacol Exp Ther* 2004; 309:275–284; 2. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; 3. FILSPARI™ FDA US PI (2/23).

TRAVERE THERAPEUTICS

Effects of ET_AR and AT_1R in the Pathophysiology of Glomerular Disease*

Sparsentan blocks the actions of ET-1 and Ang II[1]

Mediators including ET-1/Ang II

Glomerular injury

Complement activation

Complement activation[6]

Glomerular blood flow[3,7]

Tubulointerstitial inflammation & fibrosis

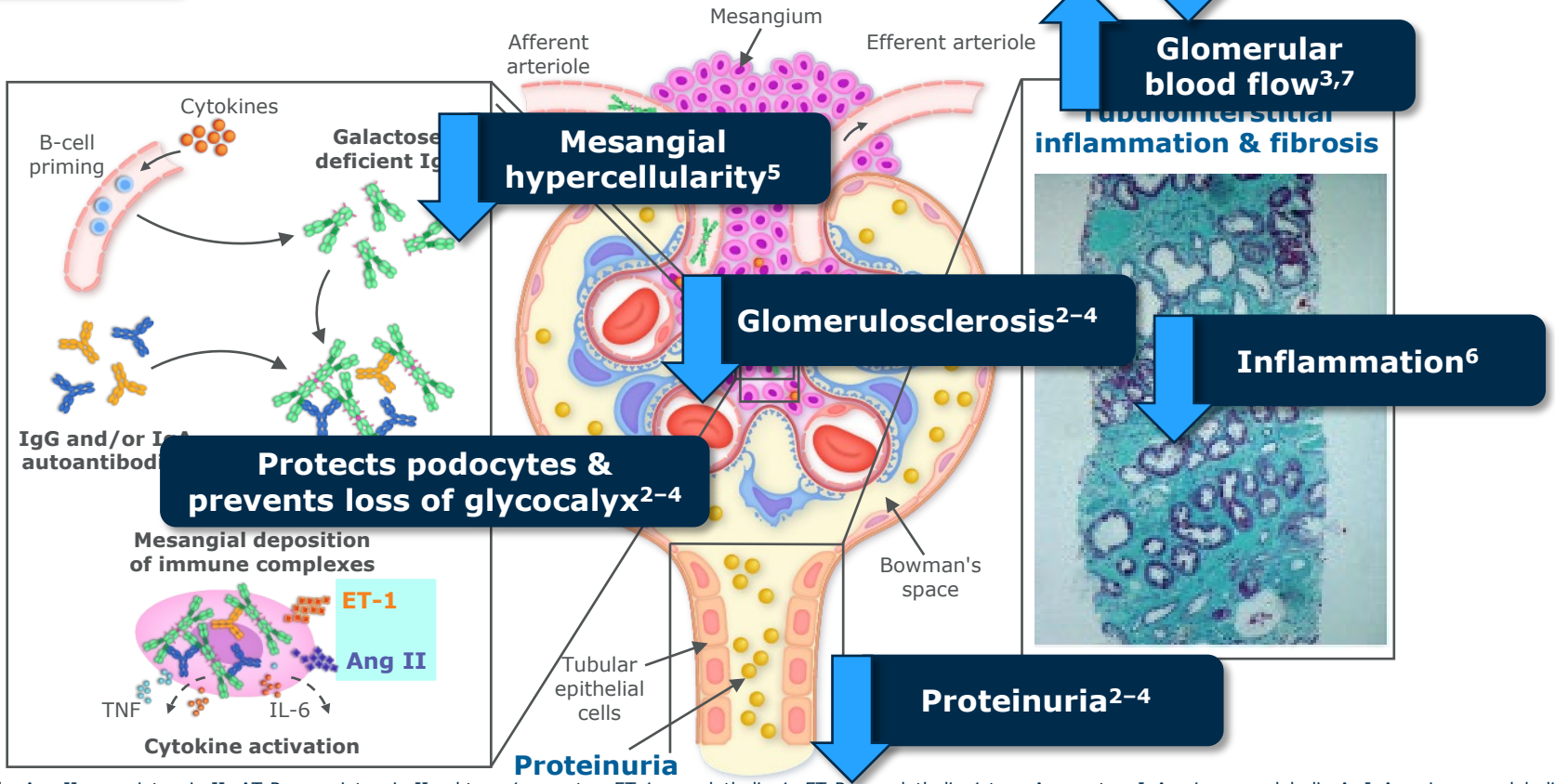
Mesangial hypercellularity[5]

Glomerulosclerosis[2–4]

Inflammation[6]

Protects podocytes & prevents loss of glycocalyx[2–4]

Proteinuria[2–4]



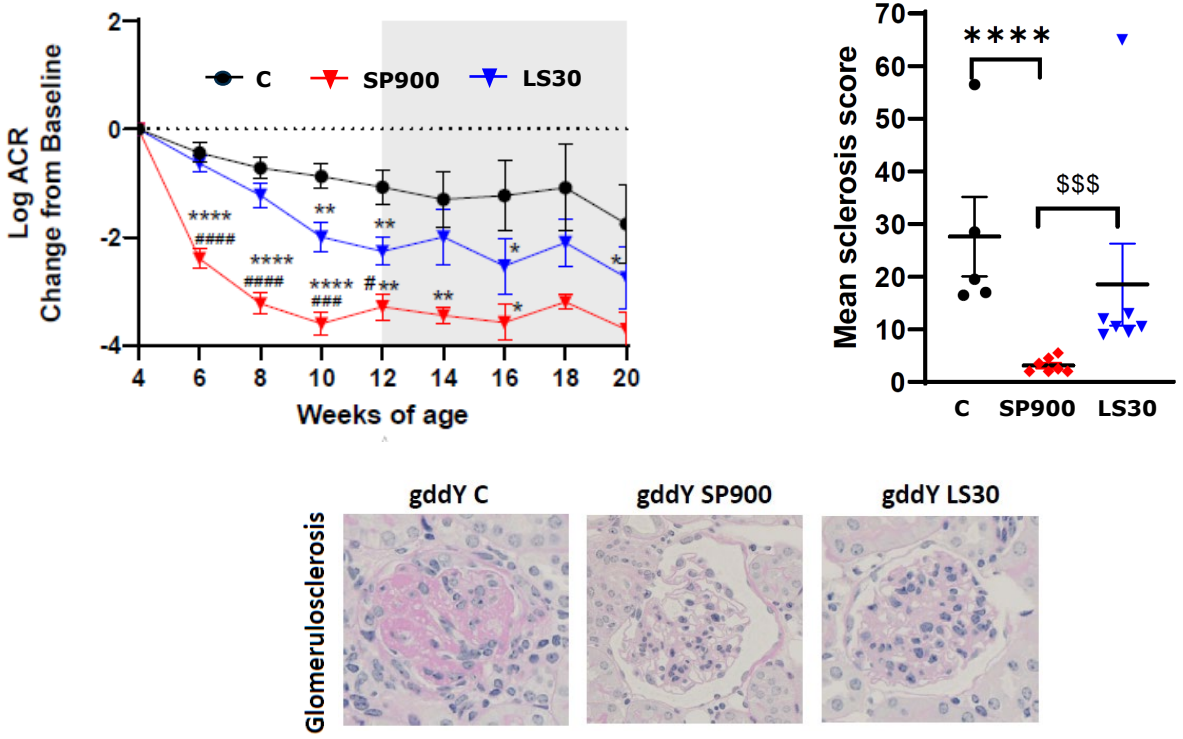
* Data from experimental animal models. Ang II = angiotensin II; AT_1R = angiotensin II subtype 1 receptor; ET-1 = endothelin-1; ET_AR = endothelin-1 type A receptor; IgA = immunoglobulin A; IgA_1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor. 1. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; 2. Nagasawa H, *et al*. ERA-EDTA 2022; oral presentation (abstract MO261); 3. Gyarmati G, *et al.* ERA-EDTA 2021; oral presentation (abstract FC016); 4. Bedard P, *et al.* ERA-EDTA 2022; oral presentation (abstract MO255); 5. Jenkinson C, *et al.* WCN 2019; poster presentation (abstract SAT-010); 6. Reily C, *et al.* ASN 2021; poster presentation (abstract PO1454); 7. Kowala MC, *et al. J Pharmacol Exp Ther* 2004; 309:275–284. Figure references: Wyatt RJ & Julian BA. *N Engl J Med* 2013; 368:2402–2414; Suzuki H, *et al. J Am Soc Nephrol* 2011; 22:1795–1803; Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; 310:R877–R884; Kohan DE & Barton M. *Kidney Int* 2014; 86:896–904; Maillard N, *et al. J Am Soc Nephrol* 2015; 26:1503–1512; Donadio J, *et al. N Engl J Med* 2002; 347:738–748. Tubulointerstitial inflammation & fibrosis image from: Cao Y, *et al. Dis Markers* 2019; 2019:2424751.

TRAVERE THERAPEUTICS

Sparsentan Attenuated Albuminuria and Glomerulosclerosis in Experimental IgA Nephropathy

The effect of sparsentan on albuminuria and glomerulosclerosis in gddY mice over 16 weeks of treatment

Effect of sparsentan on albuminuria and glomerulosclerosis[†]



Sparsentan significantly attenuated albuminuria compared with control- ($p<0.0001$) and losartan-treated mice ($p<0.001$) (over 10 weeks of treatment*)

Sparsentan significantly reduced glomerulosclerosis compared with control- ($p<0.0001$) and losartan-treated mice ($p<0.001$)

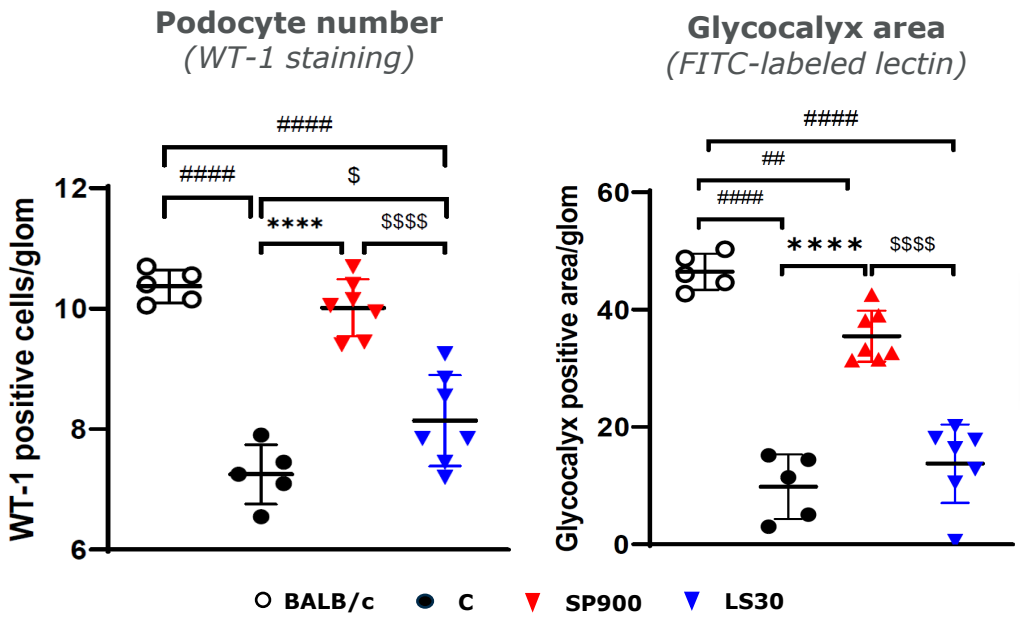
**** $p<0.0001$; ** $p<0.01$; * $p<0.05$ compared with gddY C; #### $p<0.0001$; ### $p<0.001$; # $p<0.05$ compared with gddY SP900 compared with LS30; $$$ $p<0.001$. * UACR data shown to 20 weeks; however, n=4–5 mice/gp were removed at 12 weeks of age for analysis of renal pathology; † gddY C, control n=10 (4–12 weeks of age), n=4 (12–20 weeks of age), gddY SP900 and LS30 n=12 (4–12 weeks of age), n=7 (12–20 weeks of age).
ACR = albumin-to-creatinine ratio; C = control; IgA = immunoglobulin A; IgG = immunoglobulin G; LS30 = losartan 30 mg/kg drinking water; SP900 = sparsentan 900 ppm in diet; UACR = urinary albumin-to-creatinine ratio.
gddY mice are prone to developing IgA nephropathy. The mice studied in the gddY mouse model develop albuminuria between 4 and 8 weeks of age; glomerular IgA, IgG, and C3 deposits; and glomerular injury.
Nagasawa H, *et al.* ERA-EDTA 2022; oral presentation (abstract MO261).

TRAVERE THERAPEUTICS

Sparsentan Demonstrated Renoprotective Effects in IgA Nephropathy

The effect of sparsentan on albuminuria and glomerulosclerosis in gddY mice over 16 weeks of treatment

Effect of sparsentan on podocytes and glycocalyx



Podocyte number was significantly increased in sparsentan-treated mice ($p<0.0001$ vs control and losartan) and similar to healthy BALB/c mice

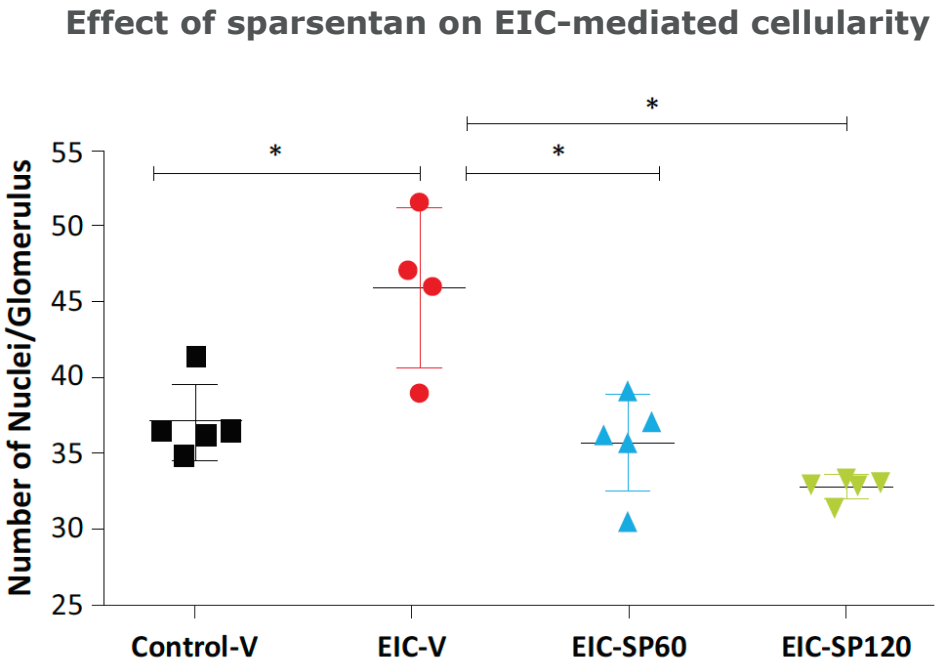
Loss of the glycocalyx area was significantly decreased in sparsentan-treated mice ($p<0.0001$ vs control and losartan)

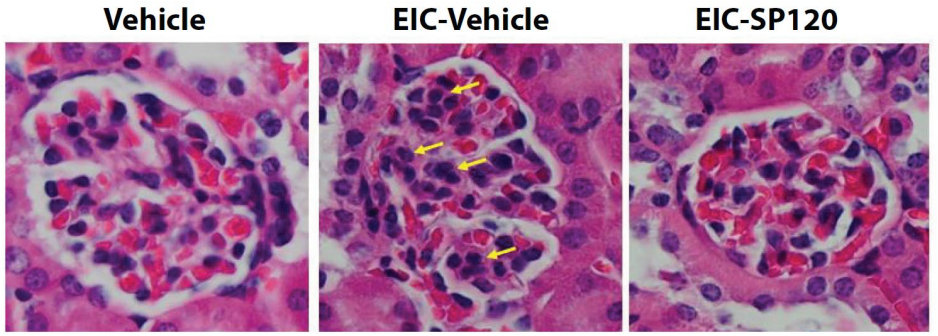
**** $p<0.0001$; #### $p<0.0001$ vs BALB/c; $ $p<0.05$; $$$ $p<0.001$; $$$$ $p<0.0001$ vs LS30.
BALB/c = healthy control mice; C = control; FITC = fluorescein isothiocyanate; IgA = immunoglobulin A; LS30 = losartan 30 mg/kg drinking water; SP900 = sparsentan 900 ppm in diet; WT-1 =Wilms tumor gene 1.
Nagasawa H, *et al.* ERA-EDTA 2022; oral presentation (abstract MO261).

TRAVERE THERAPEUTICS

Sparsentan Attenuated Glomerular Cellularity in Experimental IgA Nephropathy

The protective effects of sparsentan on a glomerular injury-induced mouse model of IgA nephropathy*





Arrows indicate the areas with increases in cellularity in the glomerulus from the EIC-V mouse

EIC-mediated increase in cellularity (shown by number of nuclei/glomerulus) was significantly attenuated in mice treated with sparsentan at doses 60 and 120 mg/kg ($p<0.05$ vs EIC-V)

* Gd-IgA_1 and rIgG (200 mg Gd-IgA_1 and 100 mg rIgG) were used to form EIC in murine serum and were intravenously injected into ~7-week-old mice every other day for a total of 6 doses. Sparsentan was given by oral gavage once daily at 60 or 120 mg/kg (SP60 or SP120) with dosing commencing on the first day of the EIC injections.
EIC = engineered immune complexes; EIC-V = mice receiving EIC injection and vehicle; Gd-IgA_1 = galactose-deficient immunoglobulin A subclass 1; IgA = immunoglobulin A; rIgG = recombinant immunoglobulin G; SP = sparsentan; V = vehicle. Jenkinson C, *et al.* WCN 2019; poster presentation (abstract SAT-010).

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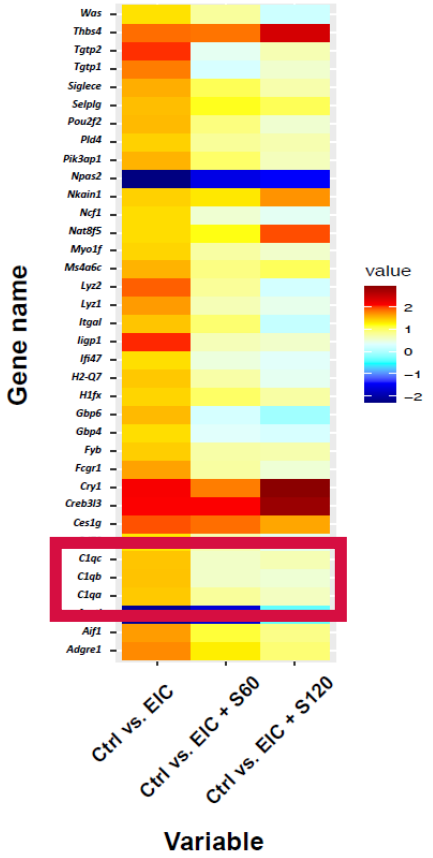
Sparsentan Downregulated the Expression of Inflammatory Genes in a Mouse Model of IgA Nephropathy

The effects of sparsentan on gene transcription in an experimental mouse model of IgA nephropathy*

Pathway-level analysis of inflammatory processes

Up Pathways		Down Pathways			
Control vs. EIC		EIC vs. EIC+S120		EIC vs. EIC+S60	
Pathway	p value	Pathway	p value	Pathway	p value
Cytokine signaling	2.53E-08	Cytokine signaling	2.97E-09	Cellular response to INF1	1.49E-08
Cellular response to IFN1	2.53E-08	Cellular response to INF1	3.87E-09	IFN1 signaling	1.49E-08
IFN1 signaling	2.53E-08	IFN1 signaling	3.87E-09	Cytokine signaling	2.90E-07
Neutrophil response	3.52E-05	Neutrophil response	1.24E-05	Neutrophil response	0.001
Neutrophil degranulation	6.37E-05	Neutrophil degranulation	2.40E-05	Neutrophil degranulation	0.002
Neutrophil immunity	8.22E-05	Neutrophil immunity (GO:0002446)	3.08E-05	MHC1-mediated Ag response	0.002
Cellular response to cytokine	7.33E-04	Cellular response to cytokine	0.001	Neutrophil immunity	0.002
MHC1-mediated Ag response	0.003	MHC1-mediated Ag response	0.001	Response to IFNγ	0.003
Response to IFNγ	0.004	Response to IFNγ	0.001	Response to IFNβ	0.005
Cytokine response	0.004	MHC1-mediated, TAP-dependent Ag response	0.003	MHC1-mediated, TAP-dependent Ag response	0.006



Sparsentan normalized or reversed the upregulation in gene expression for pathways associated with cytokine stimulation and immune and cellular activation

EIC-induced expression of genes in complement pathway (C1qa, C1qb, and C1qc) was downregulated with sparsentan treatment†

* EIC were injected into ~7-week-old mice every other day for a total of 6 doses (n=5/group) via tail vein; † WGCNA analysis between grouped pairs (control vs EIC, control vs EIC+S120, control vs EIC+S60) was performed to find module eigengenes that correlate with nuclei per glomerulus and Ki67 positivity. Genes from modules significantly associated with cellular phenotypes (p-adj.<0.05) were then cross-compared with DESeq2 LFC analysis. Vehicle or sparsentan (60 [S60] or 120 [S120] mg/kg) was given by gavage once daily from the first day of EIC injections. Negative-control mice only received vehicle. Ag = antigen; EIC = engineered immune complexes; IFN = interferon; IgA = immunoglobulin A; MHC = major histocompatibility; TAP = transporter associated with antigen processing. Reily C, *et al.* ASN 2021; poster presentation (abstract PO1454).

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Summary

ET-1 and **Ang II** play a key role in the **pathophysiology of IgA nephropathy**; ET-1, acting via **ET_AR**, and Ang II, acting via **AT_1R**, are involved in multiple pathophysiologic processes that lead to **kidney dysfunction and CKD**

ET-1 and **Ang II** act in tandem to amplify the **inflammatory cytokine response** and potentiate **glomerular dysfunction**, **tubulointerstitial injury**, and **vascular dysfunction**, worsening **proteinuria** and resulting in a **progressive decline** in **kidney function**

Sparsentan is a novel dual endothelin angiotensin receptor antagonist **(DEARA)**, which **attenuated albuminuria** and **glomerulosclerosis** in **preclinical studies** of **IgA nephropathy**

Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression (UP/C ≥ 1.5 g/g)[1]

1. FILSPARI™ FDA US PI (2/23).
Ang II = angiotensin II; AT_1R = angiotensin II subtype 1 receptor; CKD = chronic kidney disease; ET-1 = endothelin-1; ET_AR = endothelin-1 type A receptor; IgA = immunoglobulin A; UP/C = urinary protein-to-creatinine ratio.

TRAVERE THERAPEUTICS