Wnt/β-catenin signaling and renin-angiotensin system

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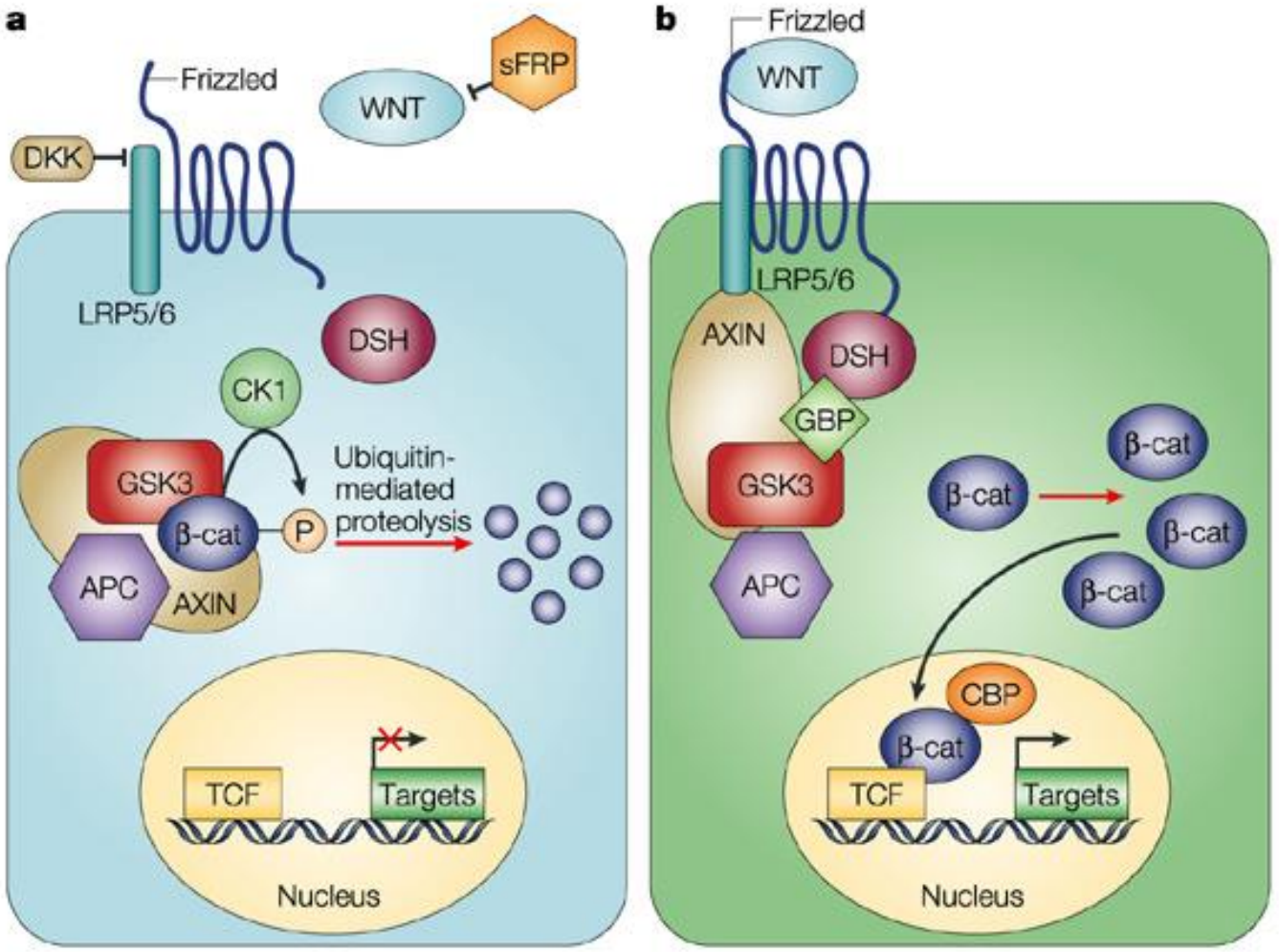
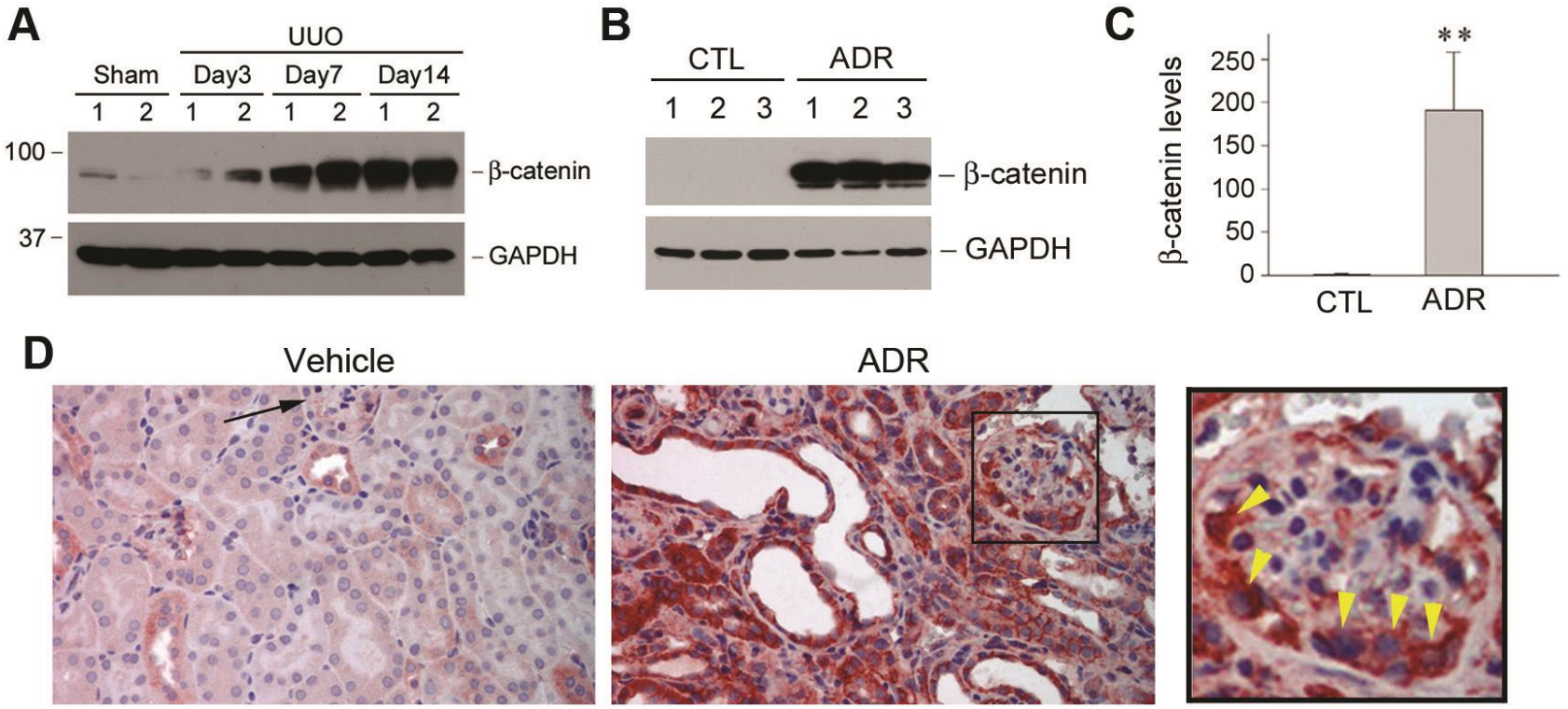
Canonical Wnt/β-catenin signaling



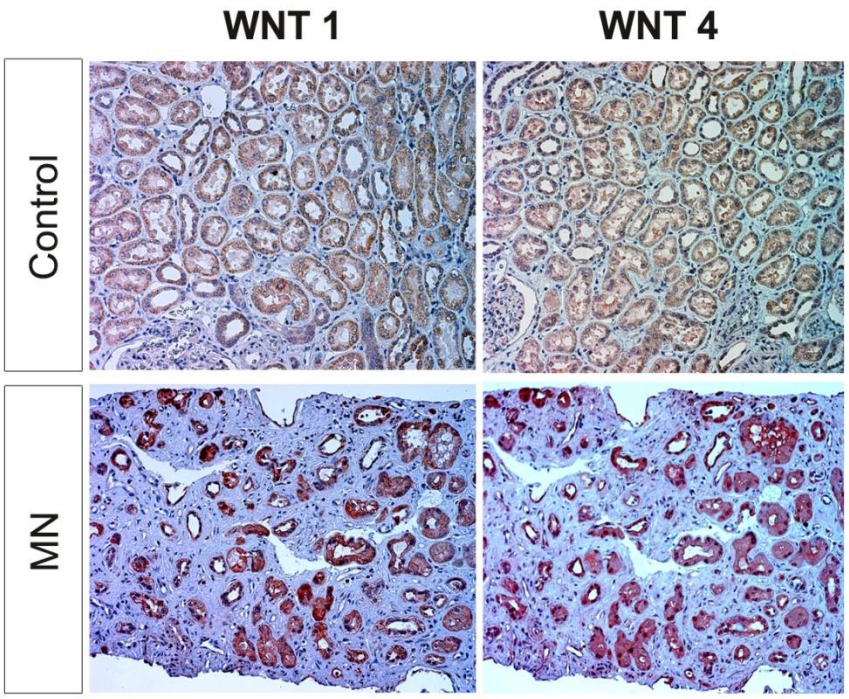
Moon et al, 2004

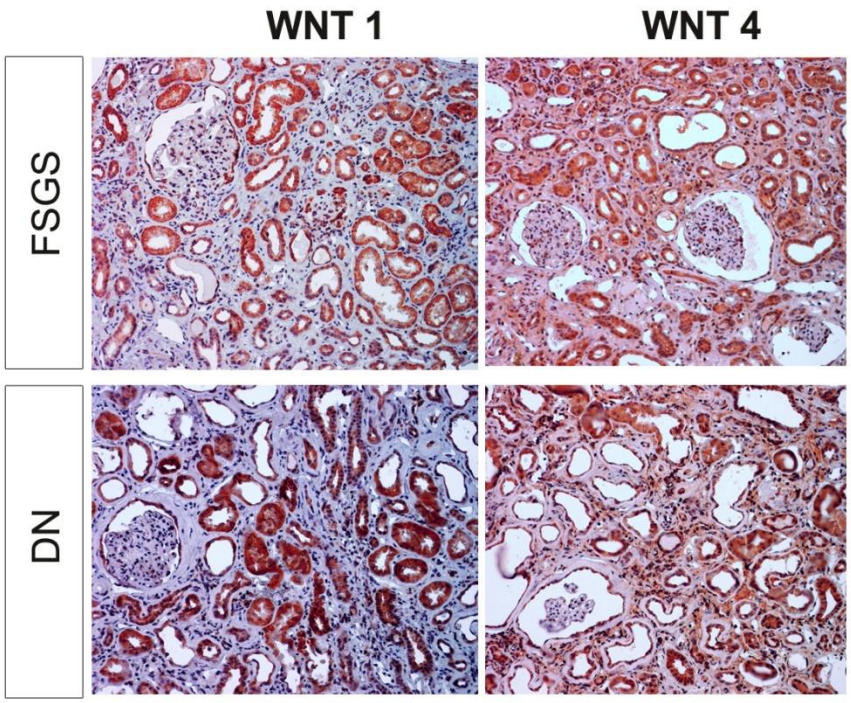
Nature Reviews | Genetics

β-Catenin is primarily induced in tubular epithelium of fibrotic kidneys

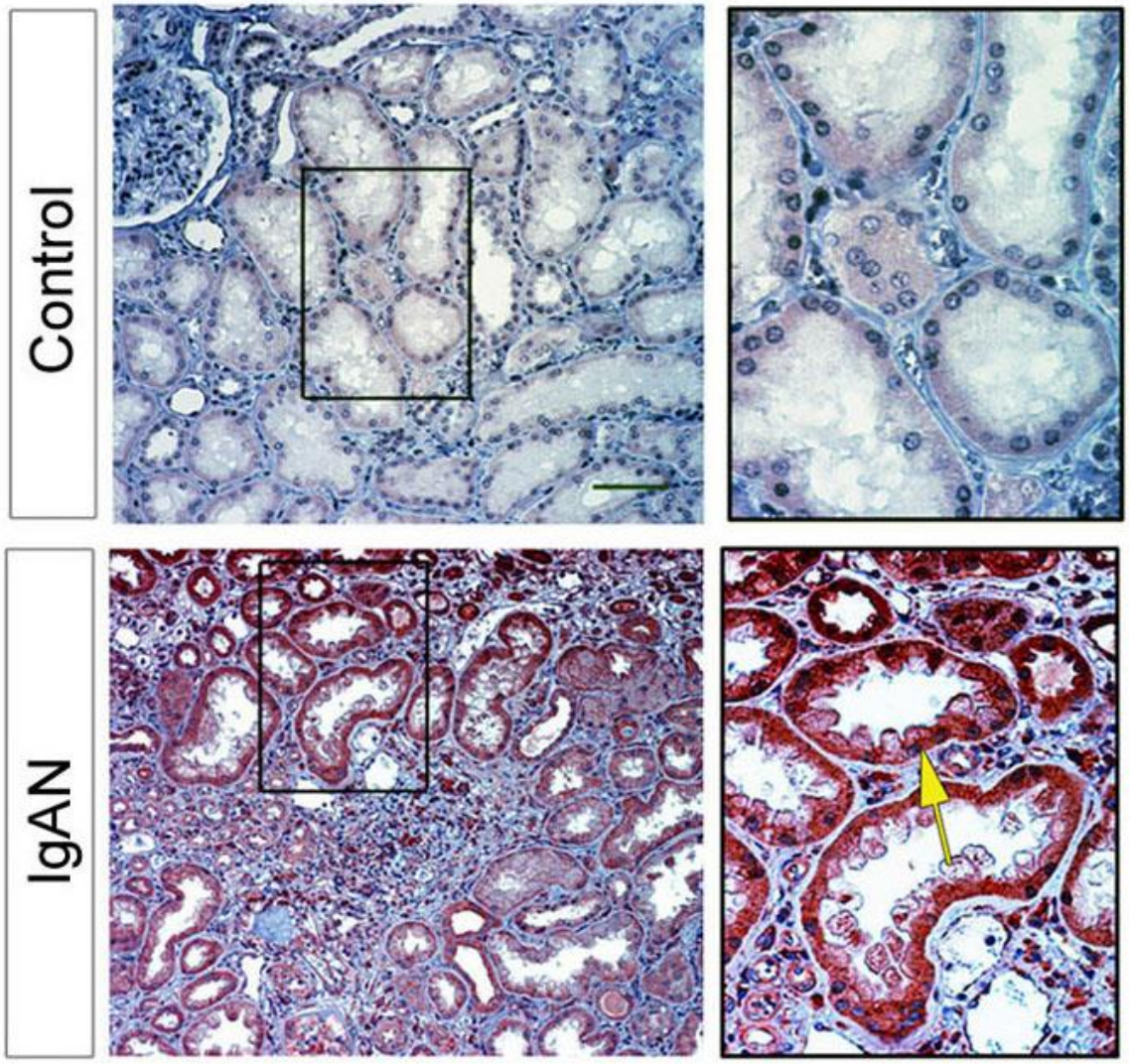


Tubular induction of Wnt1 and Wnt4 are common finding in human CKD

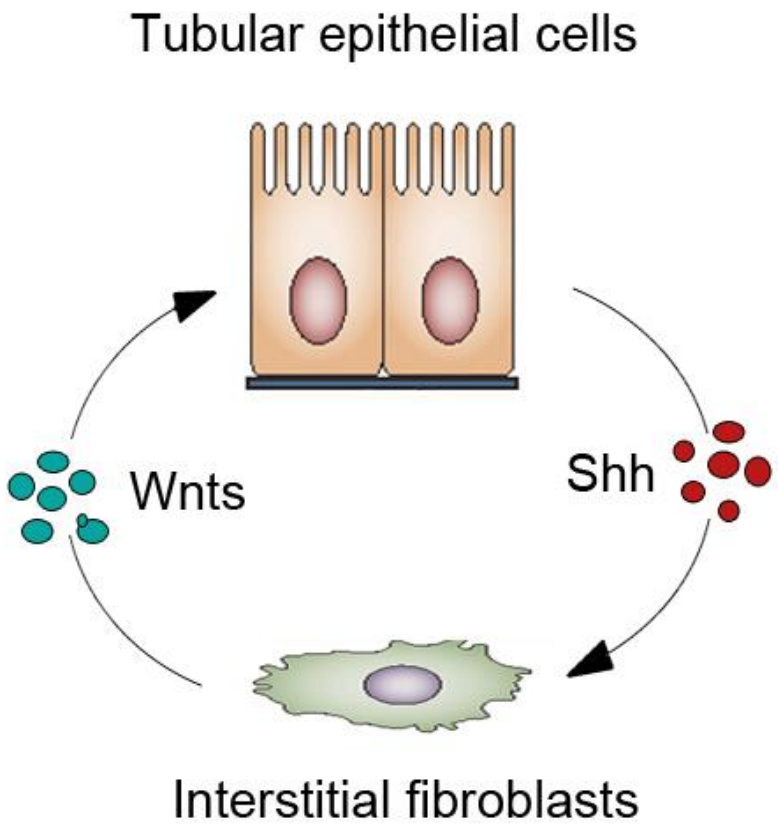




Activation of β-catenin human CKD

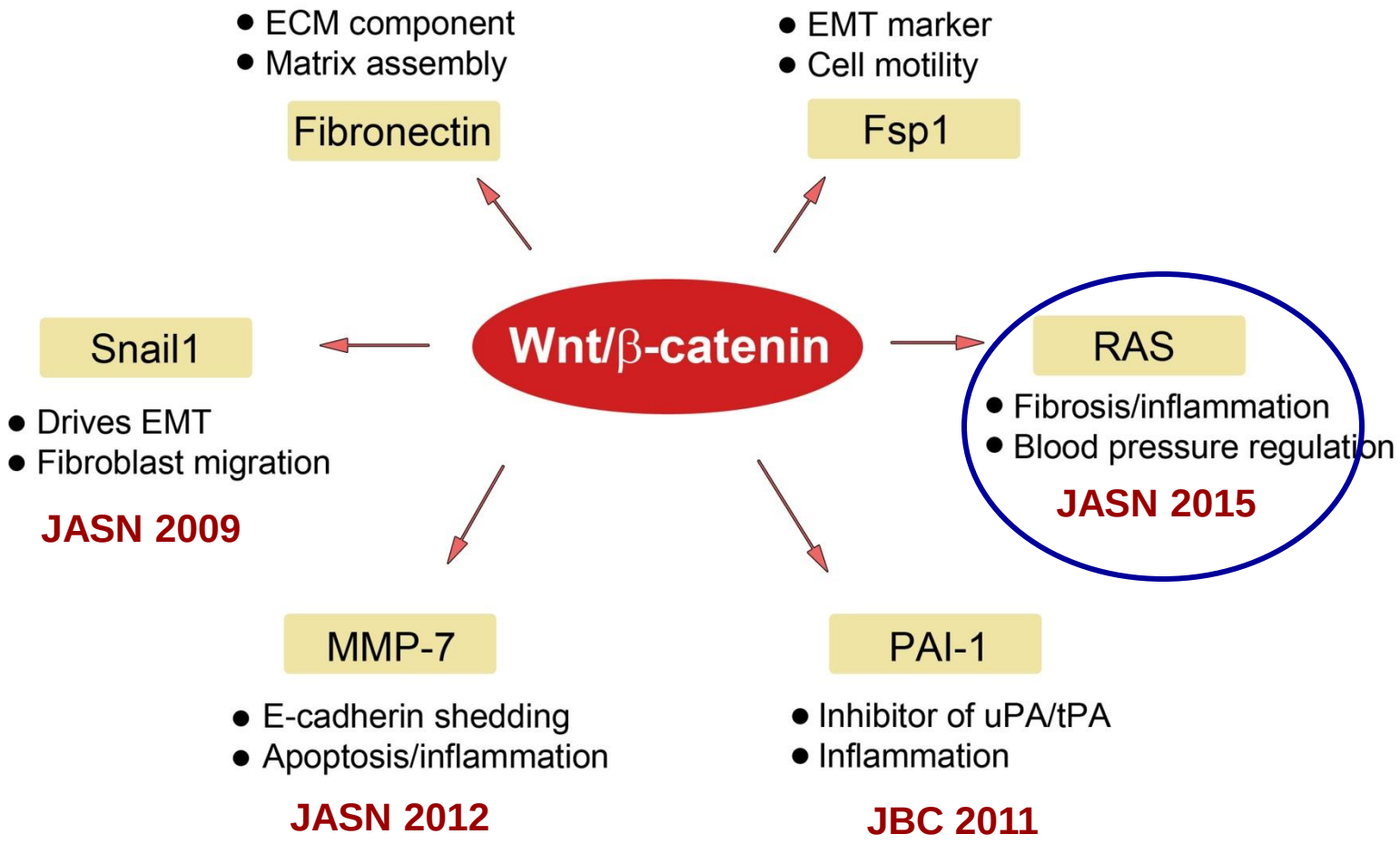


Blockade of Shh or Wnt/β-catenin signaling inhibits renal fibrosis



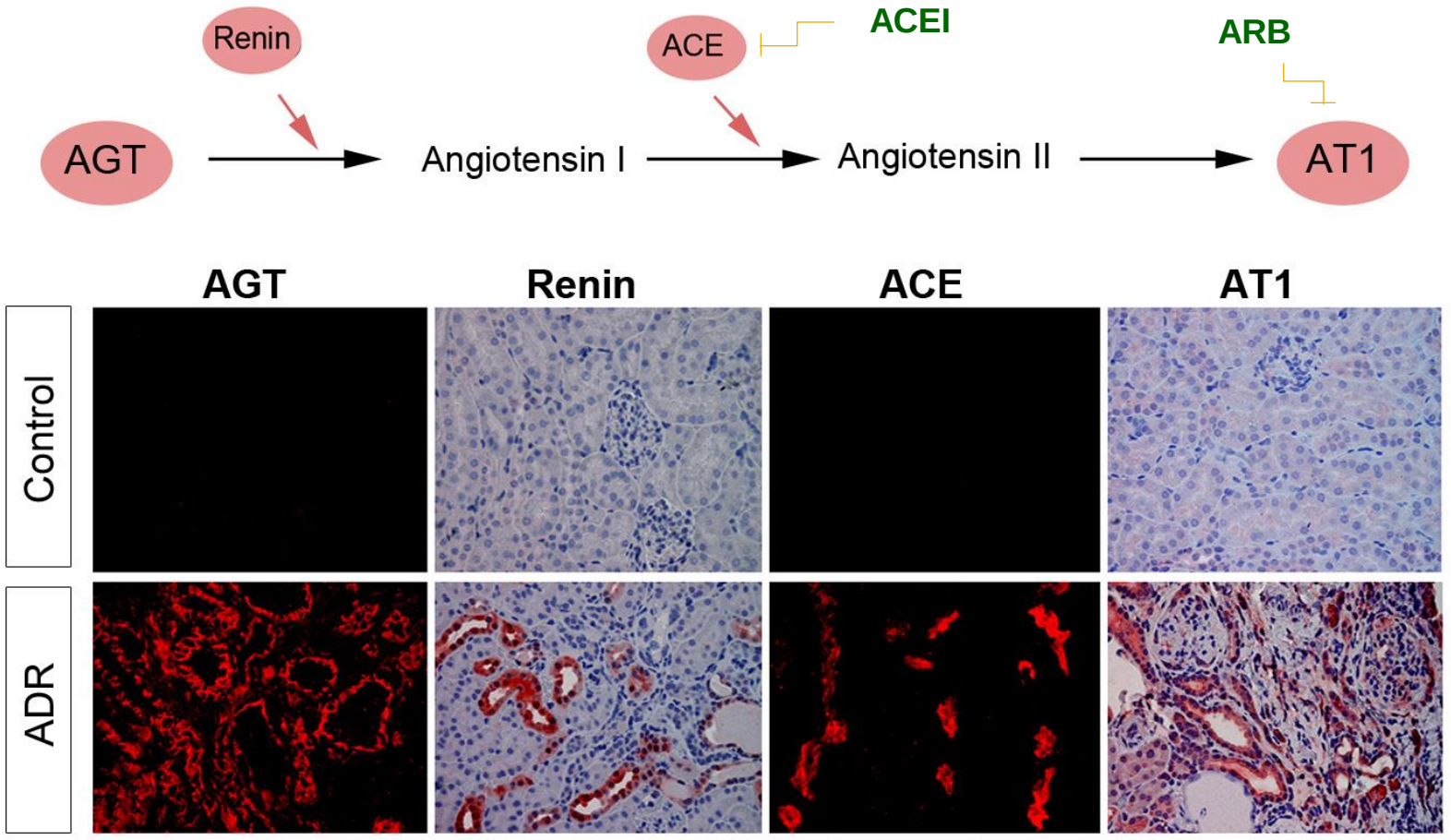
	Mode of action	
CPN	***Smo***	**JASN 2012**
		JASN 2014
DKK1	***LRP5/6***	**JASN 2009**
Paricalcitol	***VDR***	**JASN 2011**
ICG-001	***CBP***	**JASN 2011**
Klotho	***Wnt***	**JASN 2013**
ICG-001	***CBP***	**JASN 2014**

Wnt/β-catenin downstream targets

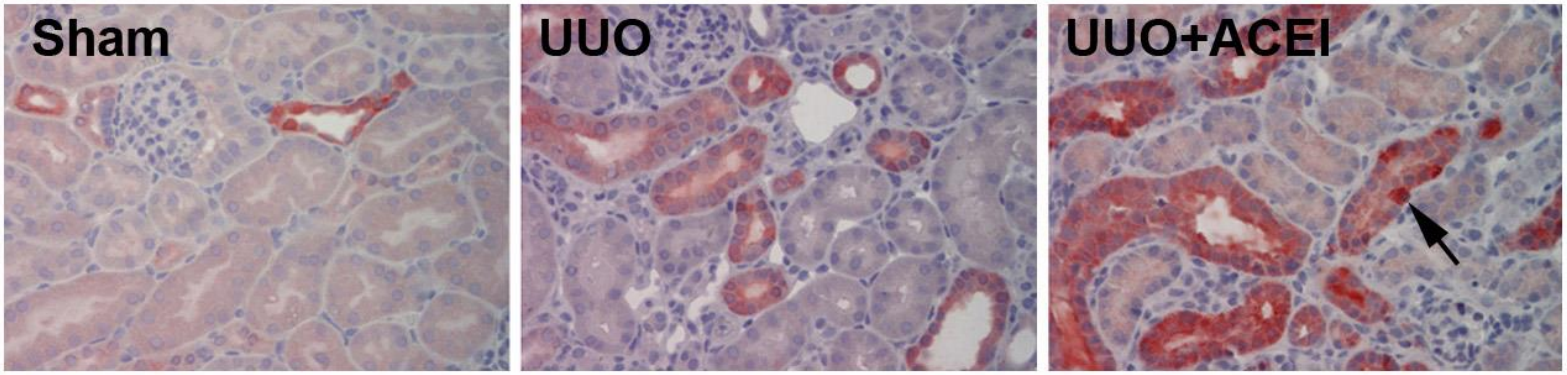


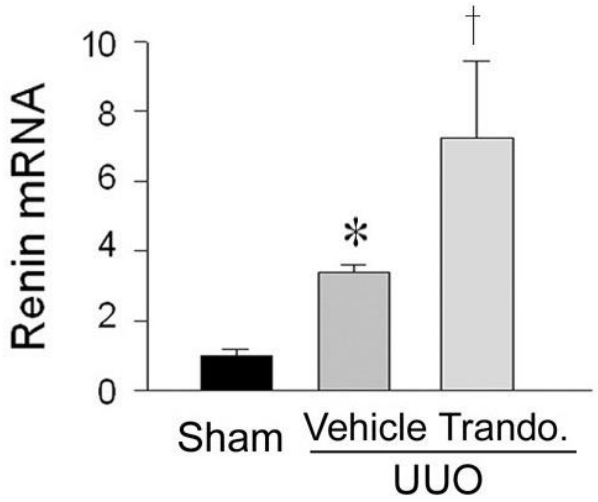
Wnt/β-catenin and RAS activation

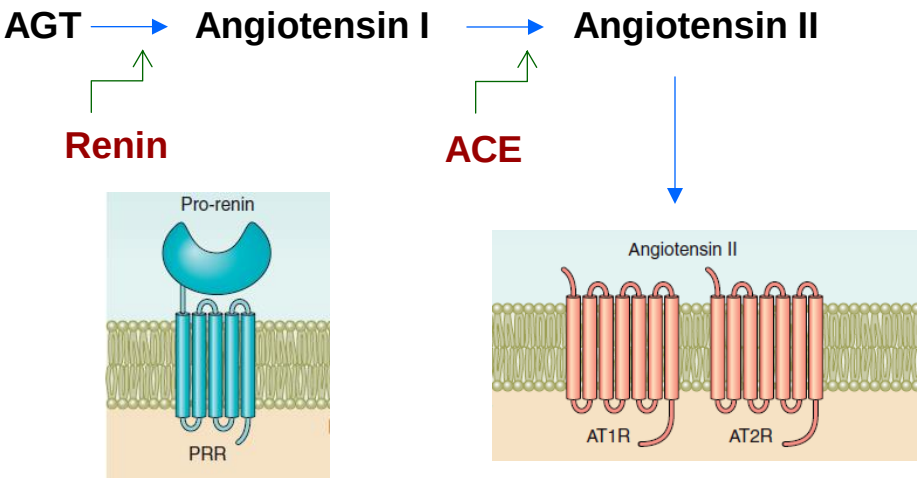
Up-regulation of multiple components of the renin-angiotensin system in CKD



Inhibition of RAS upregulates renin expression in vivo

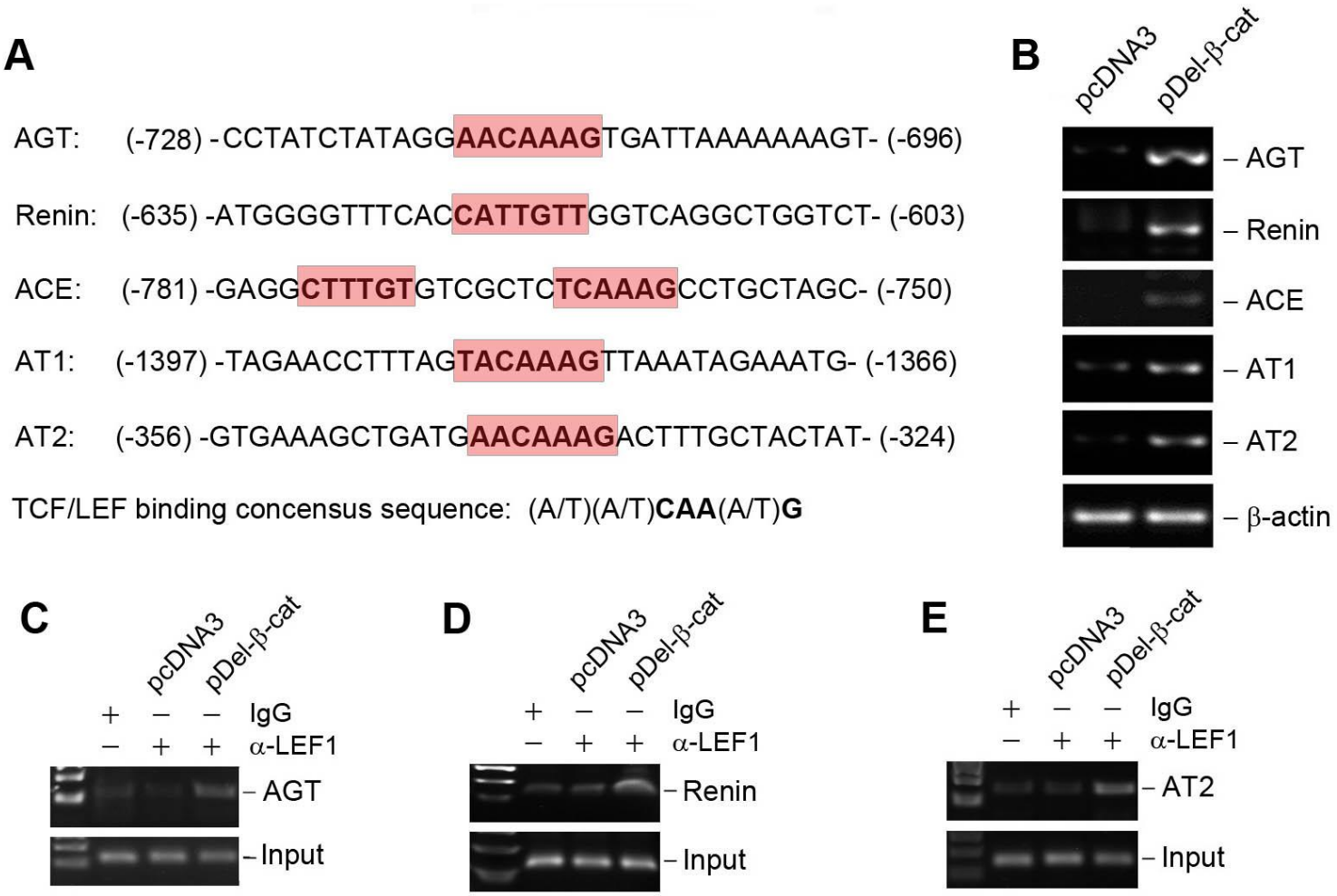




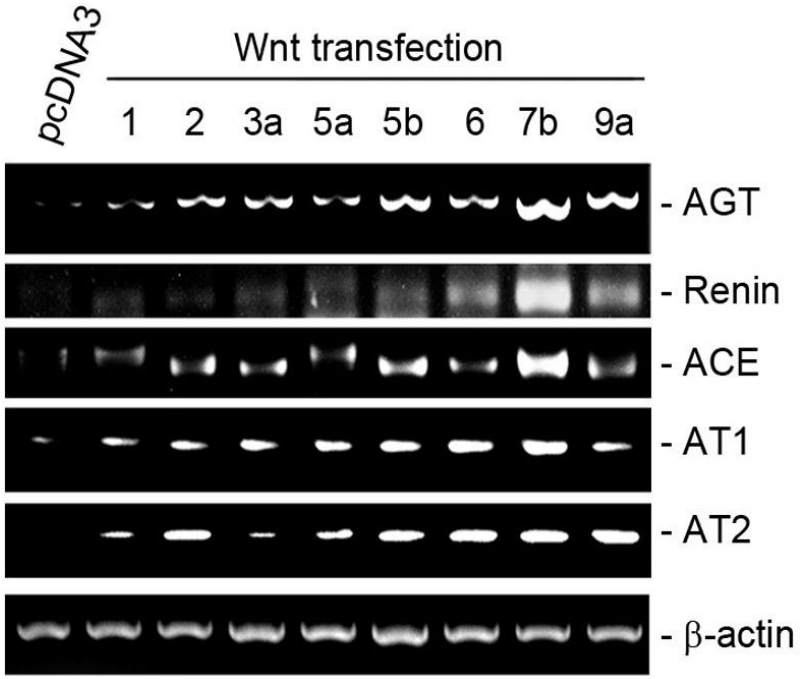


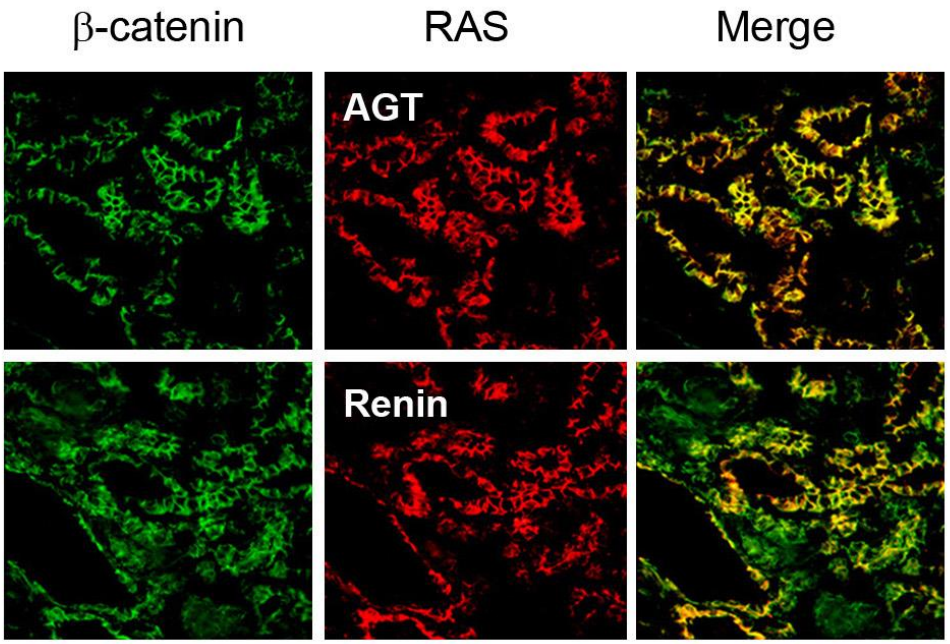
Could we simultaneously targets/inhibits multiple components of RAS?

Wnt/β-catenin signaling induces all components of renin-angiotensin system

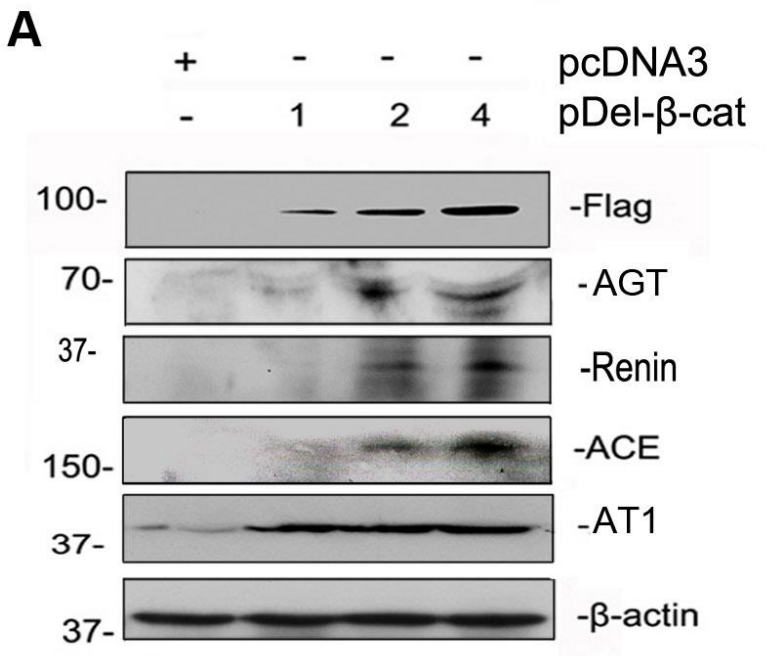


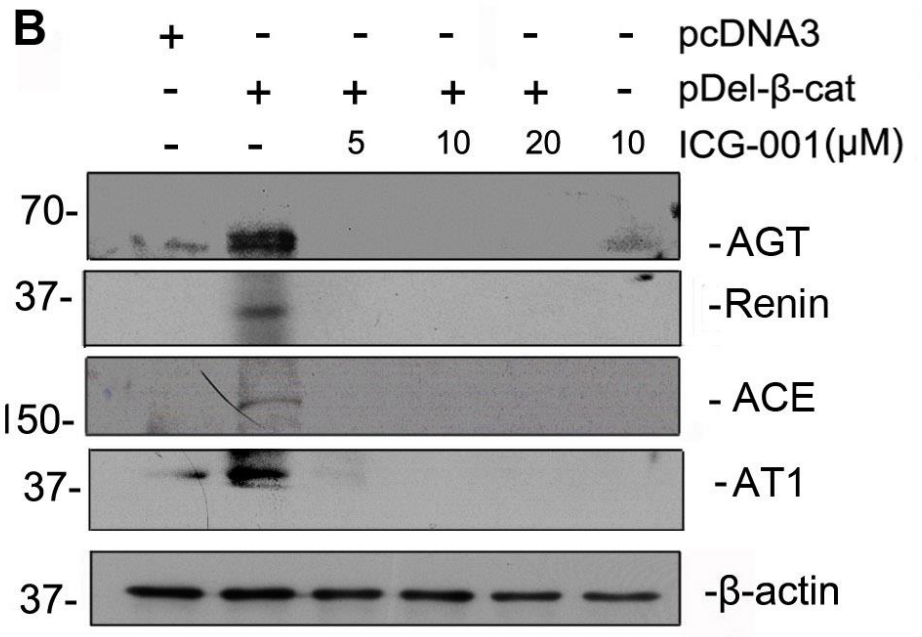
Wnt/β-catenin induces all components of RAS in vitro and localization of β-catenin and RAS in vivo



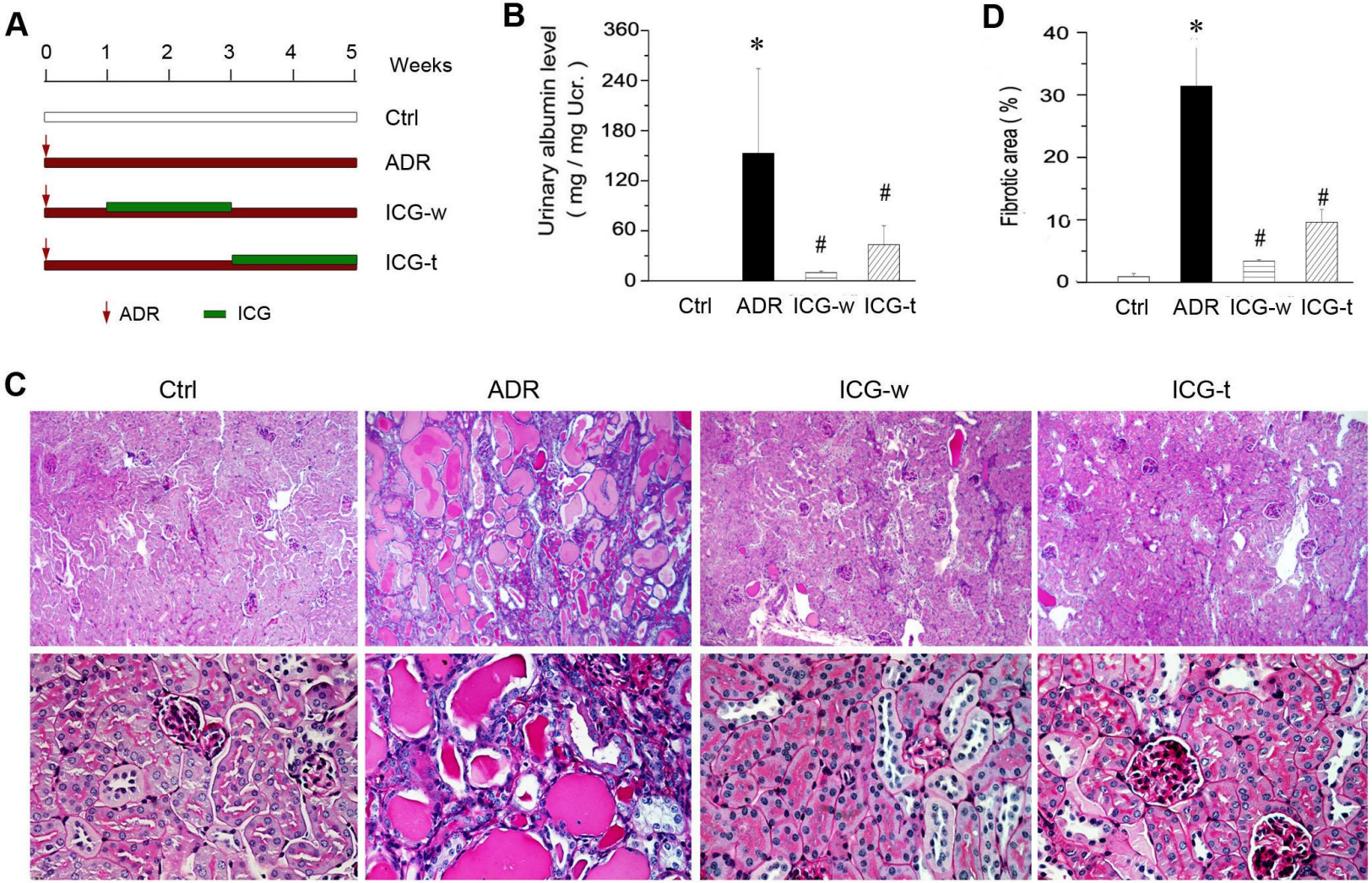


ICG-001, a specific small molecule β-catenin inhibitor, simultaneously inhibits multiple components of RAS

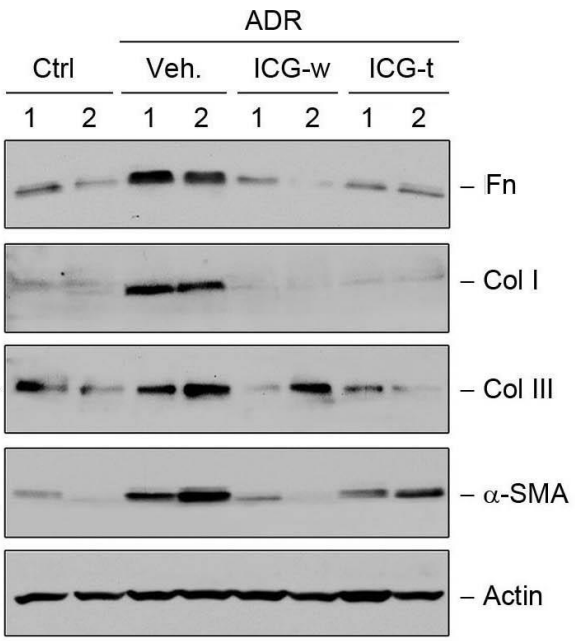


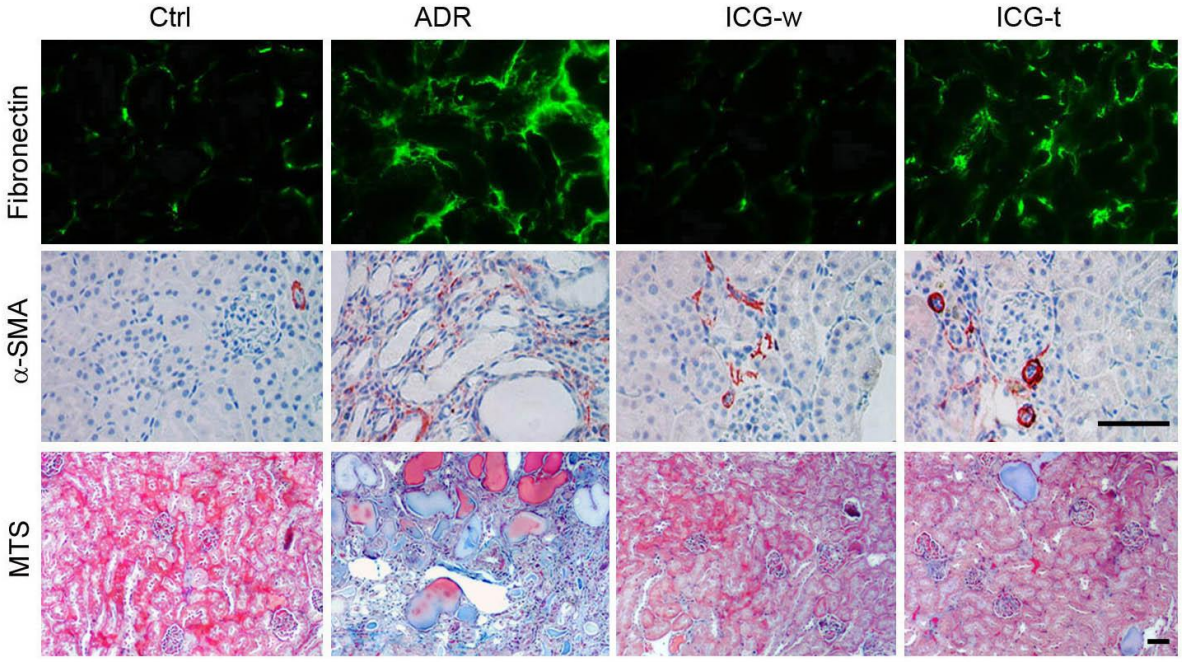


Blockade of β-catenin signaling by ICG-001 reverses proteinuria and kidney injury

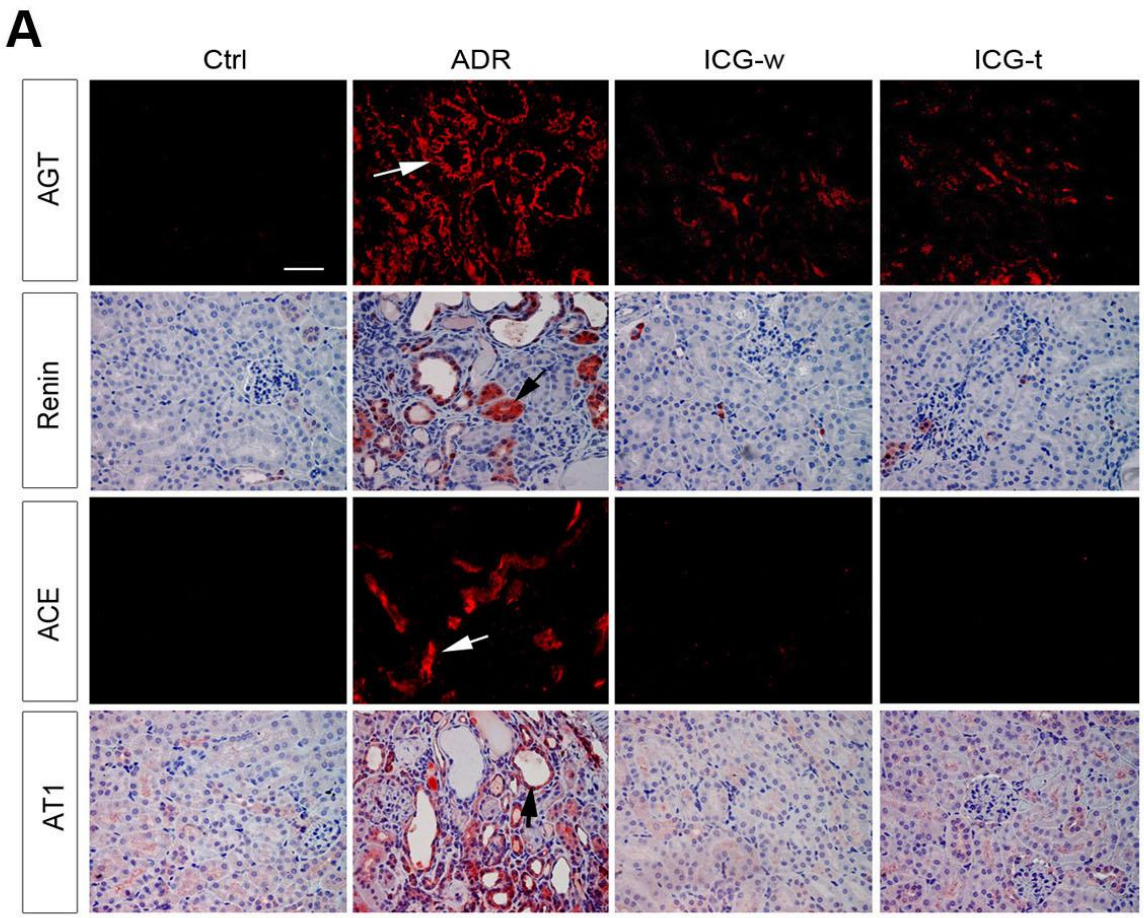


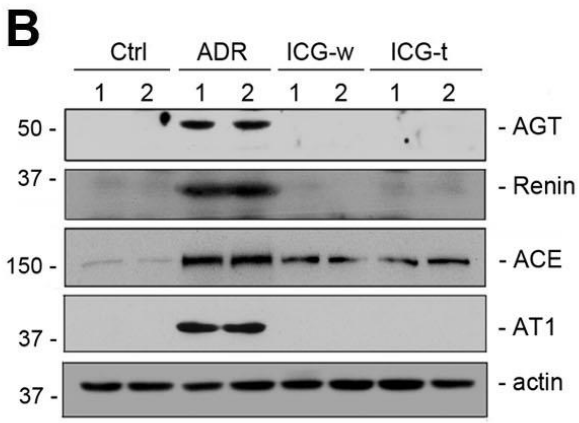
Blockade of β-catenin signaling by ICG-001 attenuates kidney fibrotic lesions

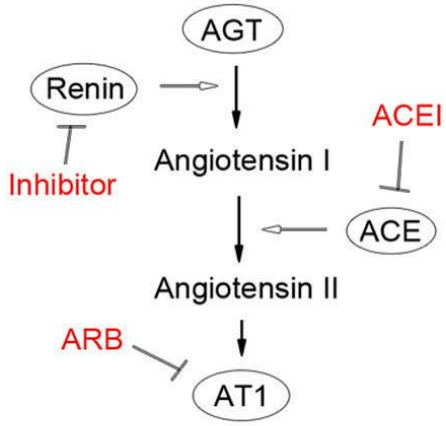




Blockade of β-catenin signaling by ICG-001 targets the expression of multiple RAS components in vivo

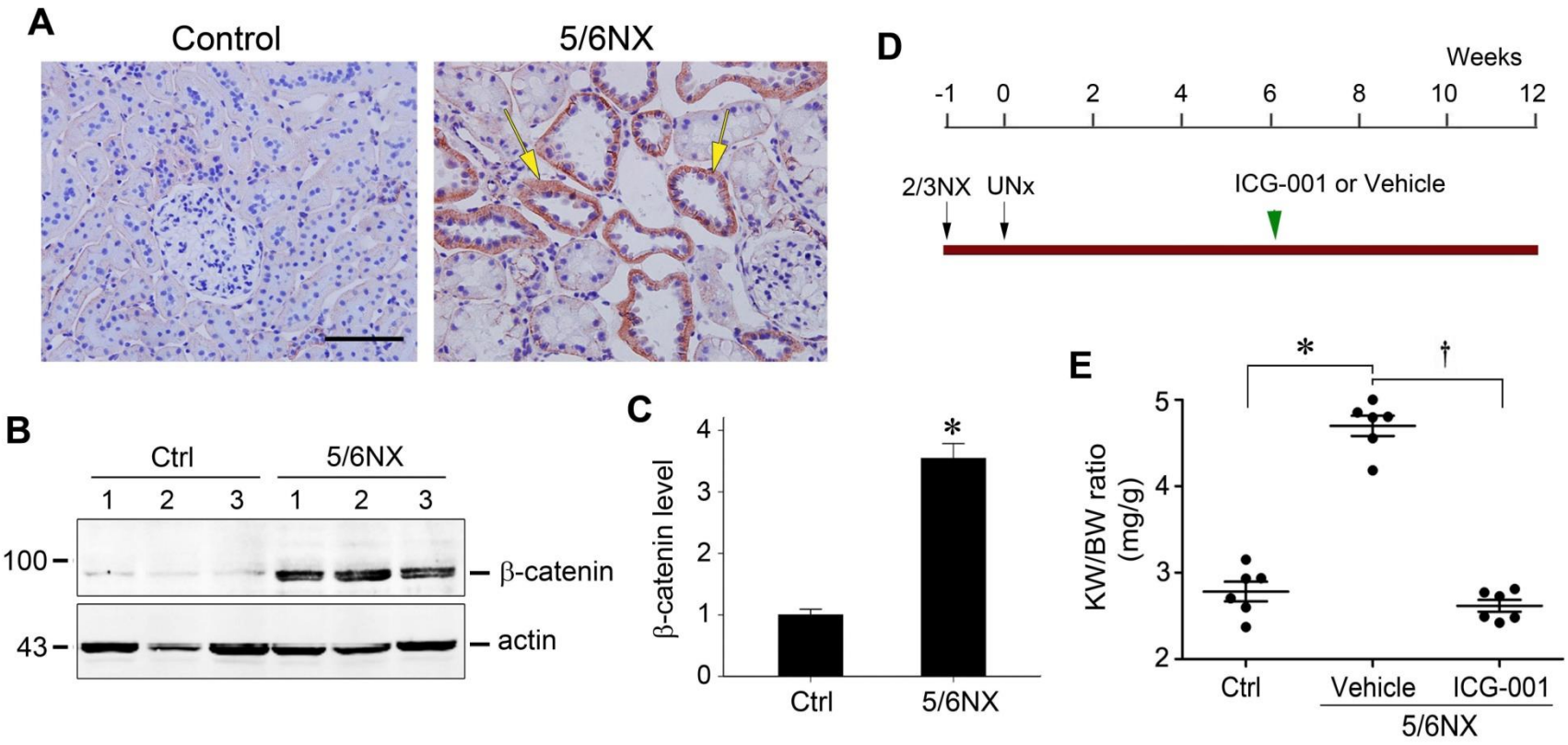






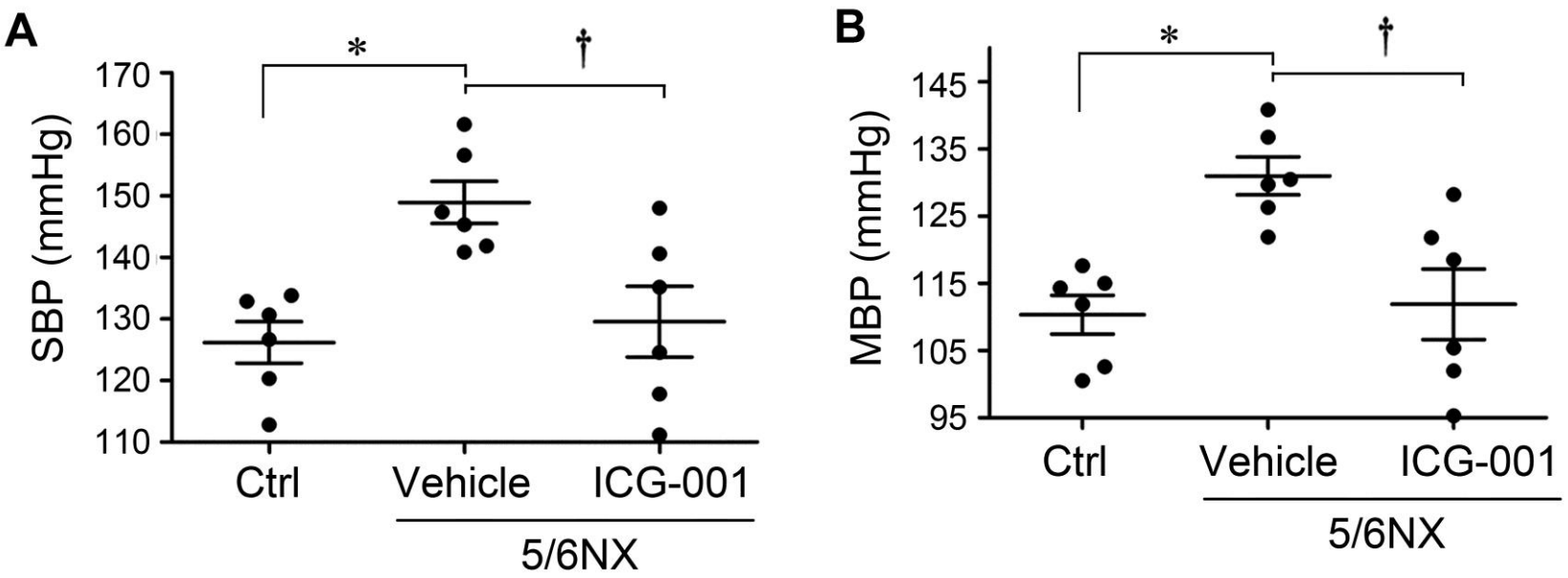
One stone kills multiple birds?

Therapeutic protocol

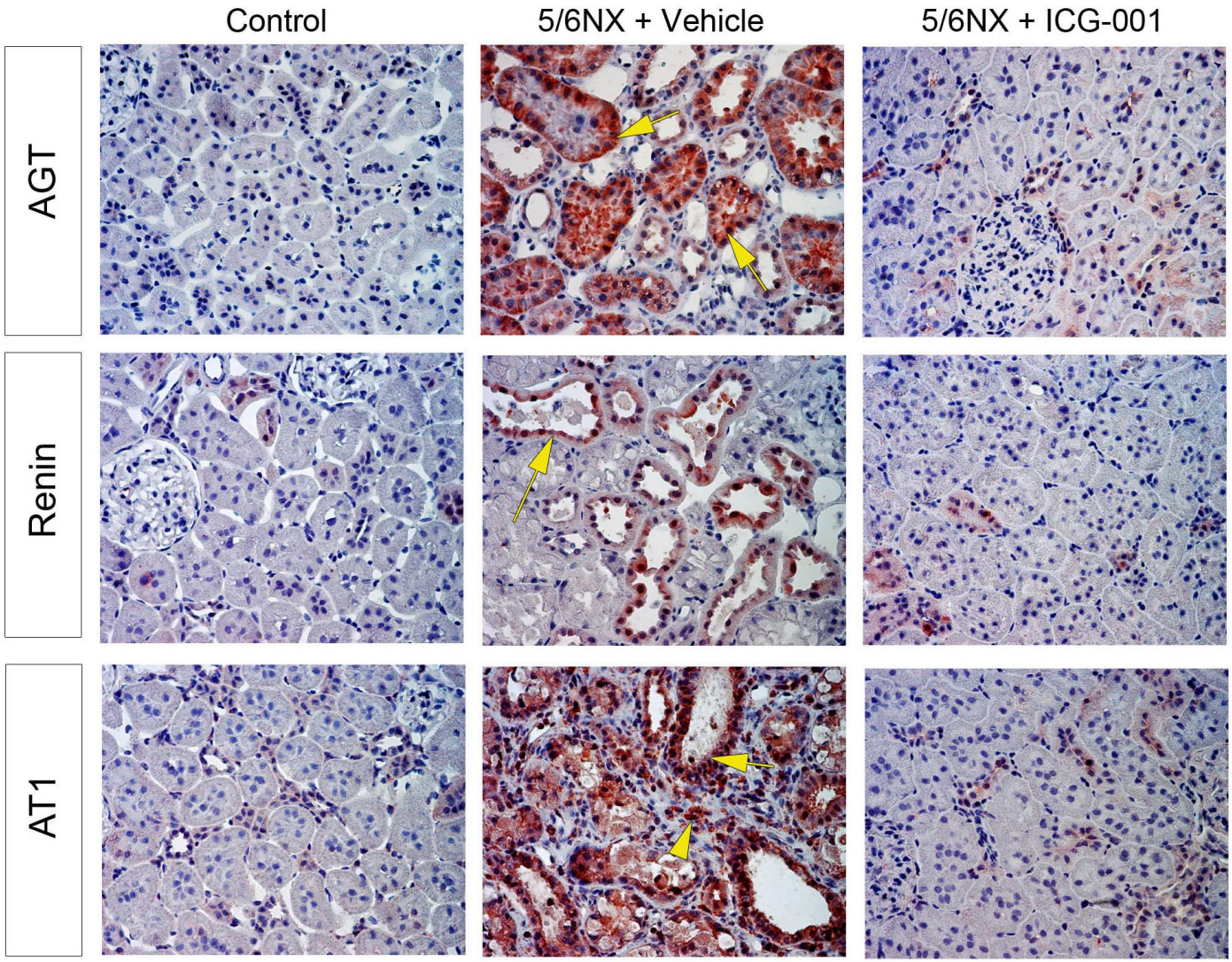


ICG-001, 3 times/week, 5 mg/kg body wt

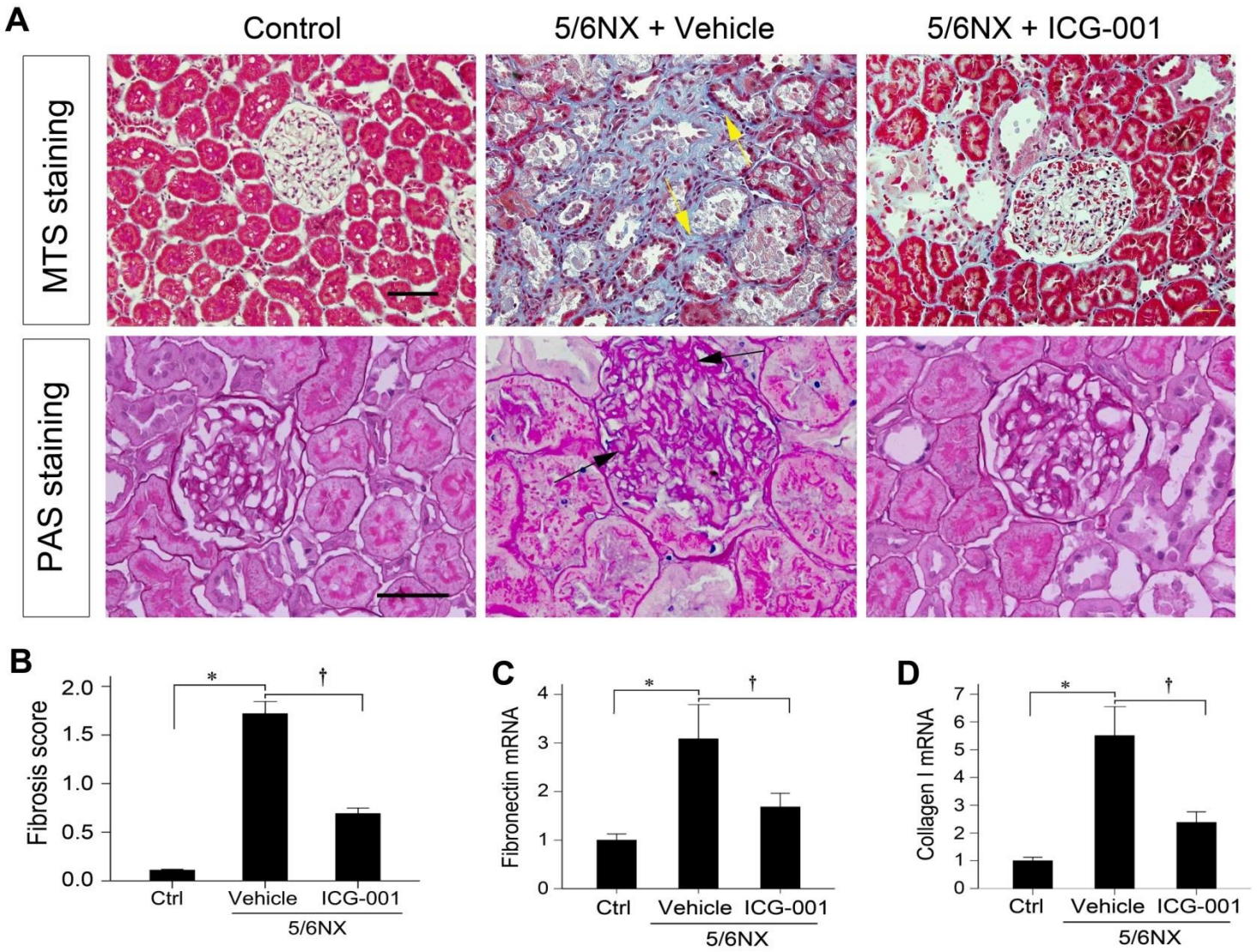
ICG-001 normalizes blood pressure in rats



ICG-001 represses RAS activation in rat remnant kidney model

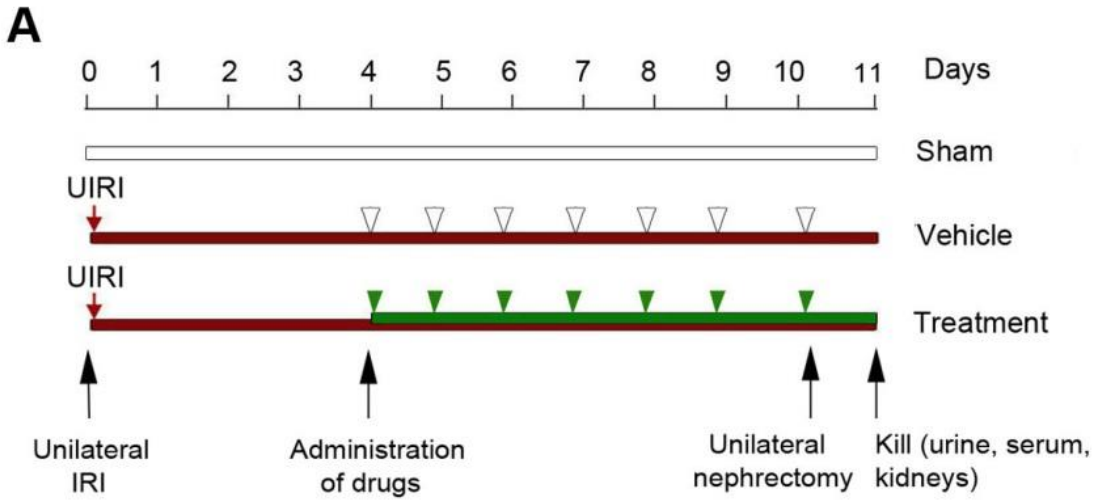


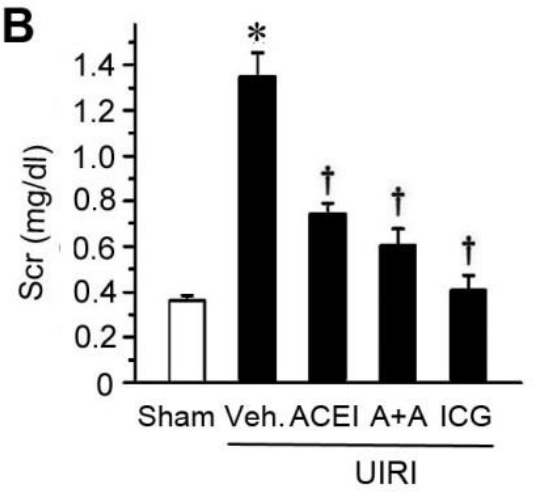
ICG-001 inhibits renal fibrosis in rat remnant kidney model

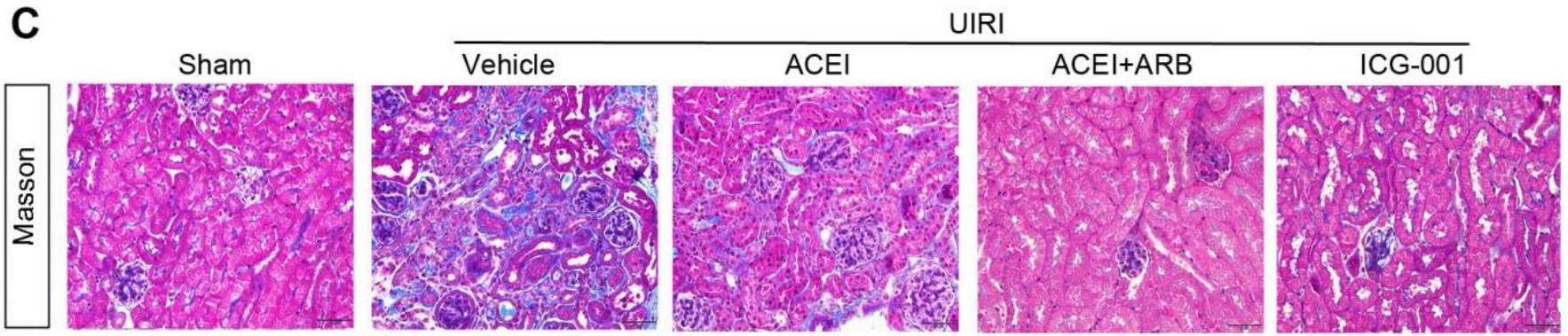


Direct comparison of the therapeutic efficacy between Wnt/β-catenin inhibitor and RAS blocker

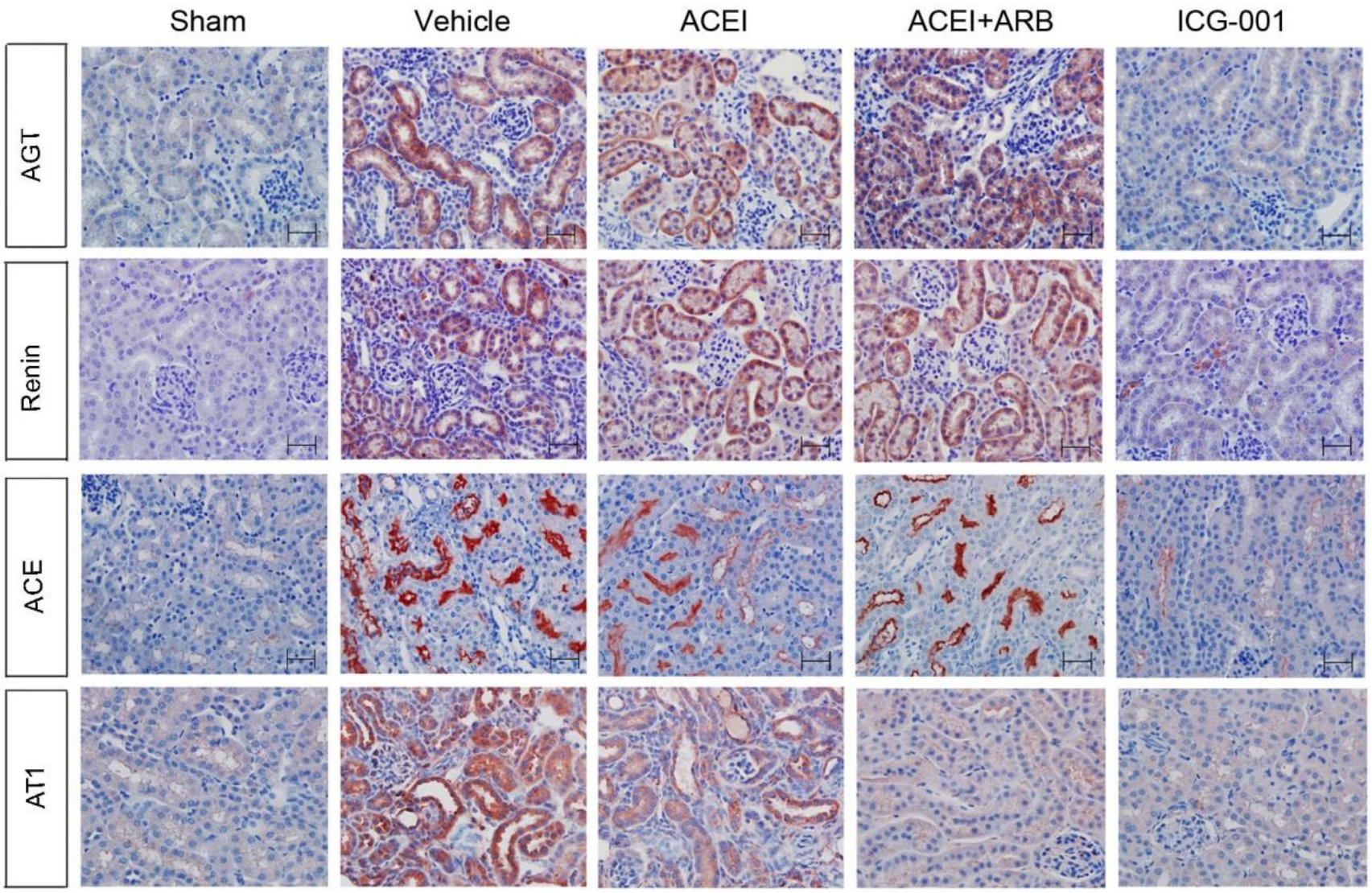
ICG-001 is more effective than RAS blocker in preventing AKI-CKD progression



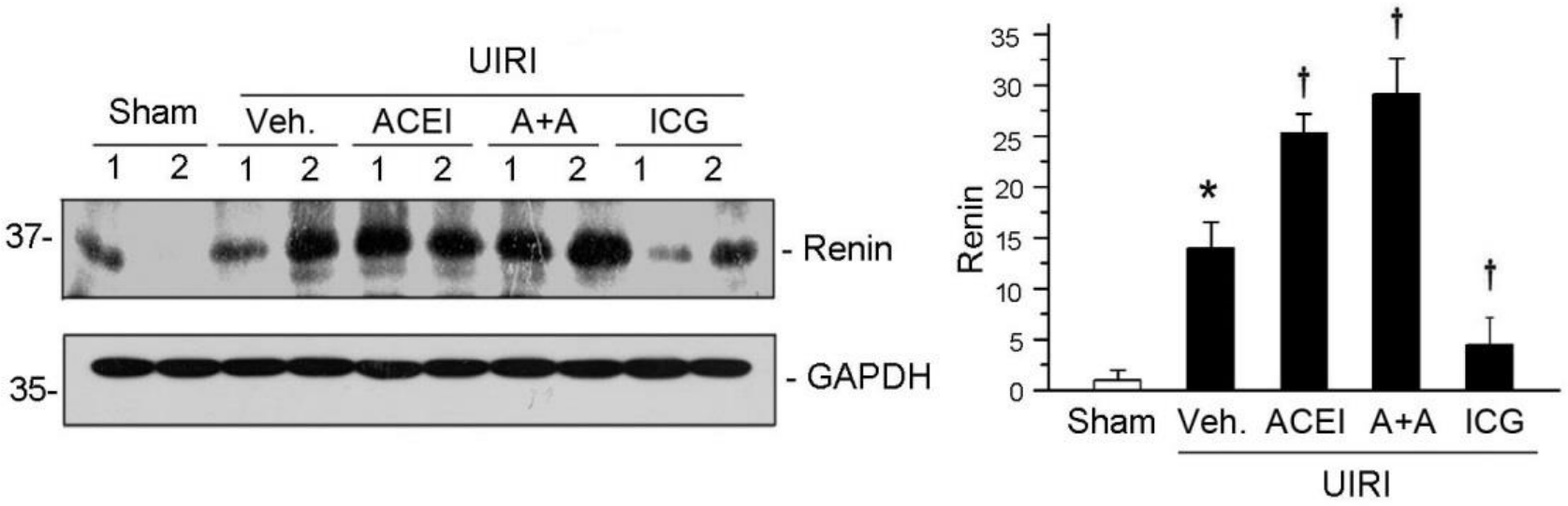




ICG-001 completely inhibits RAS expression

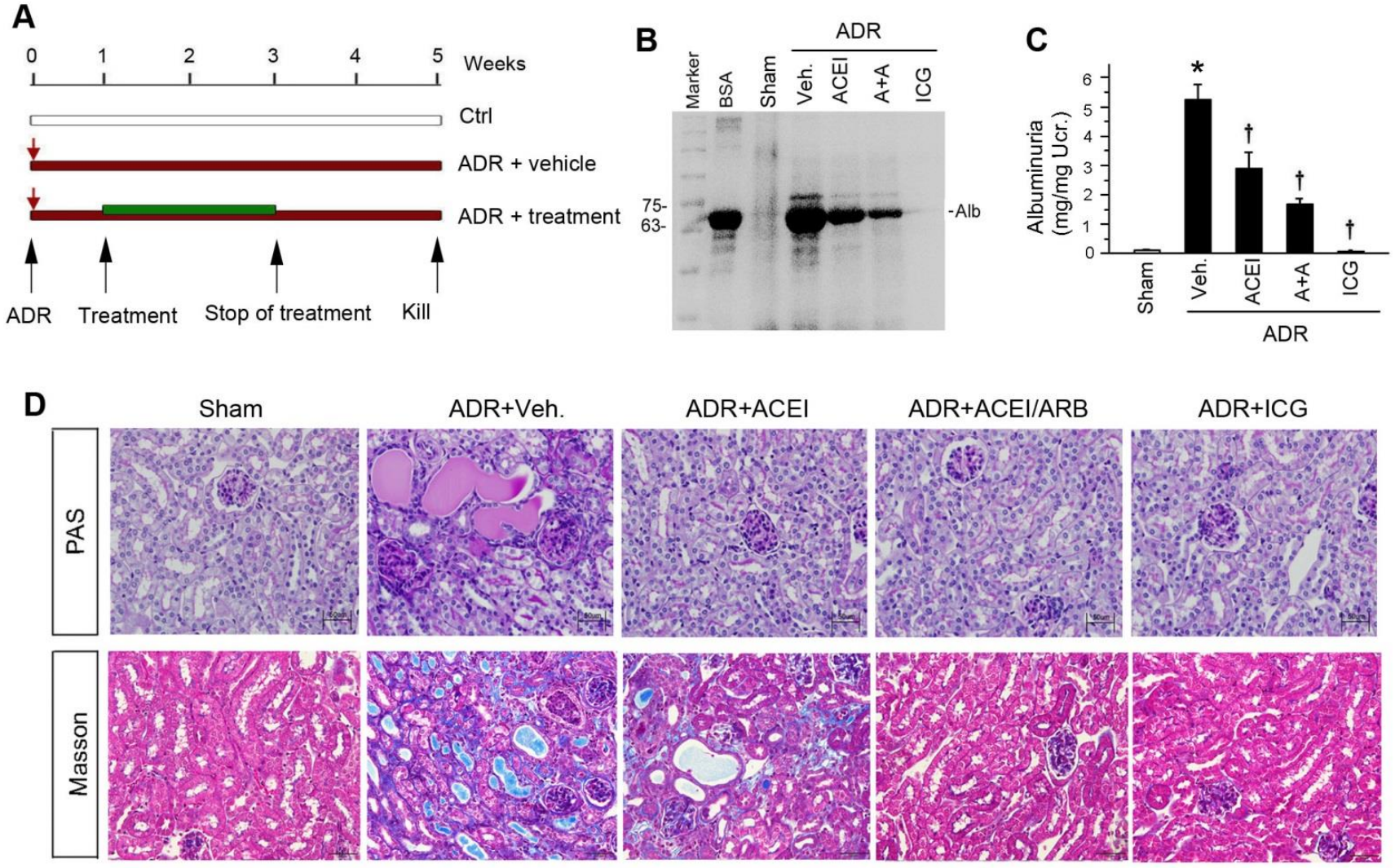


RAS blocker therapy upregulates renin expression

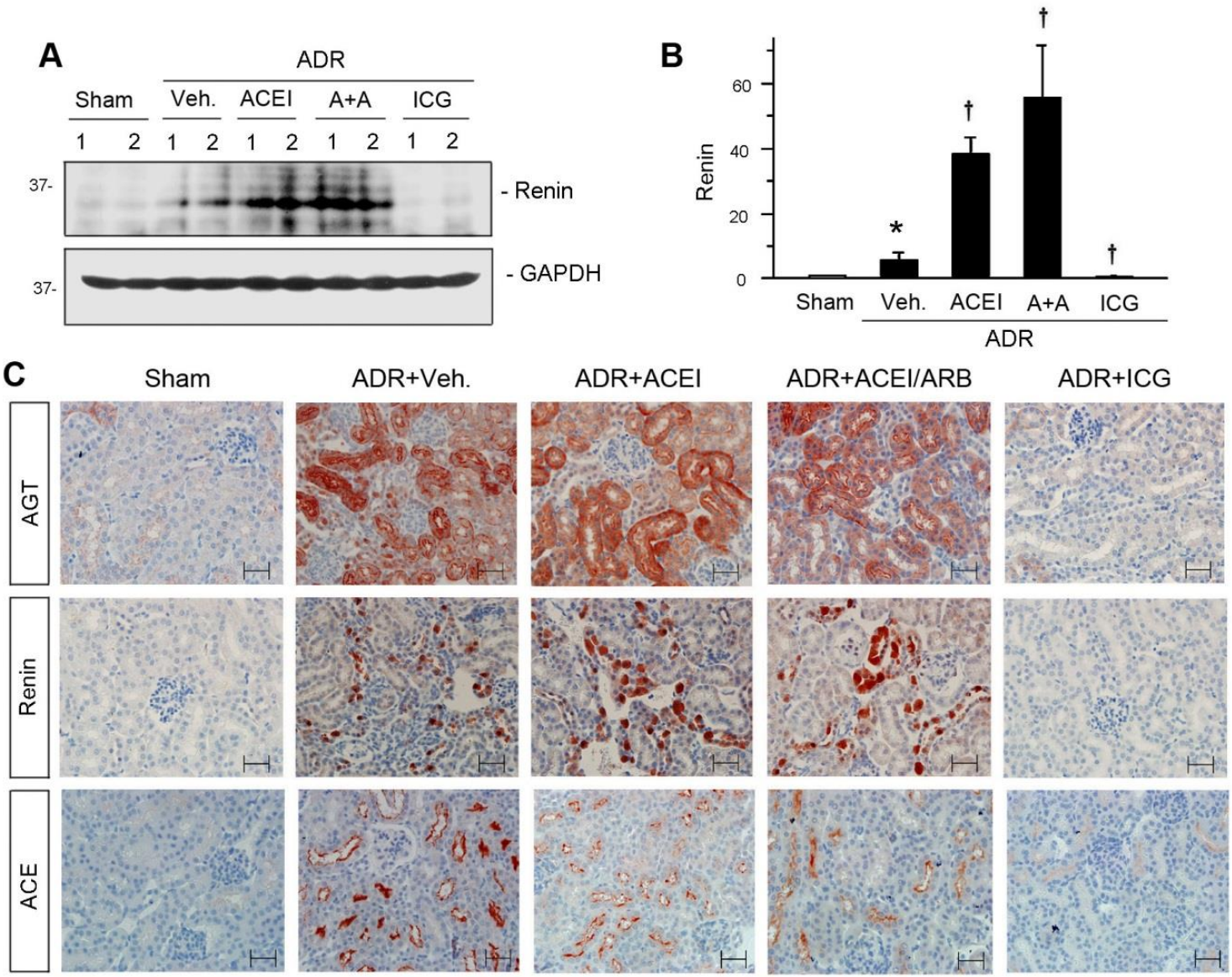


1) **Sham control**
2) **UIRI + vehicle**
3) **UIRI + trandolapril (3 mg/kg/day, oral)**
4) **UIRI + trandolapril (3 mg/kg/day, oral) + losartan (10 mg/kg/day, oral)**
5) **UIRI+ ICG-001（5 mg/kg/day, I.P.）**

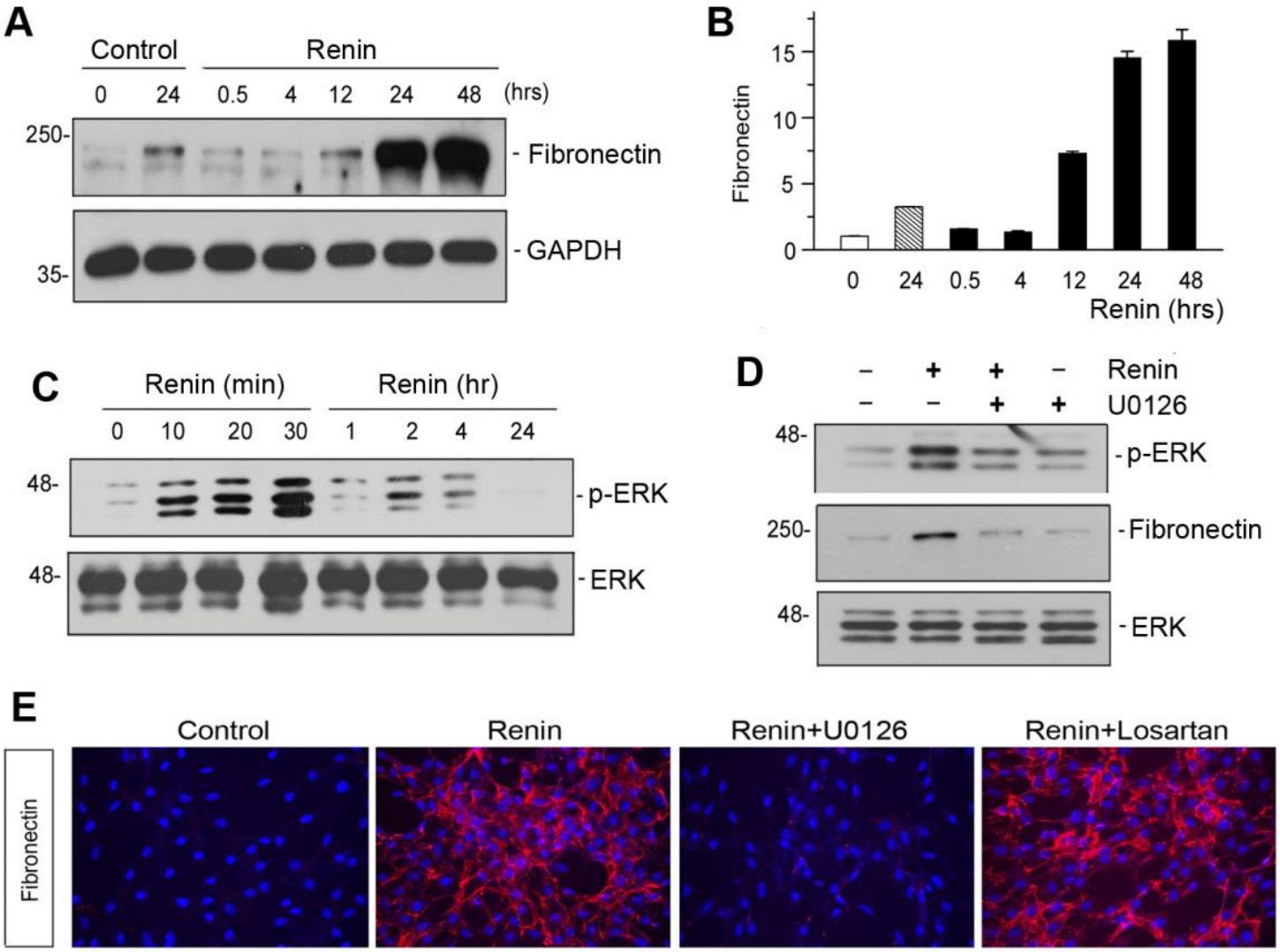
ICG-001 is more effective than RAS blocker in ameliorating ADR nephropathy



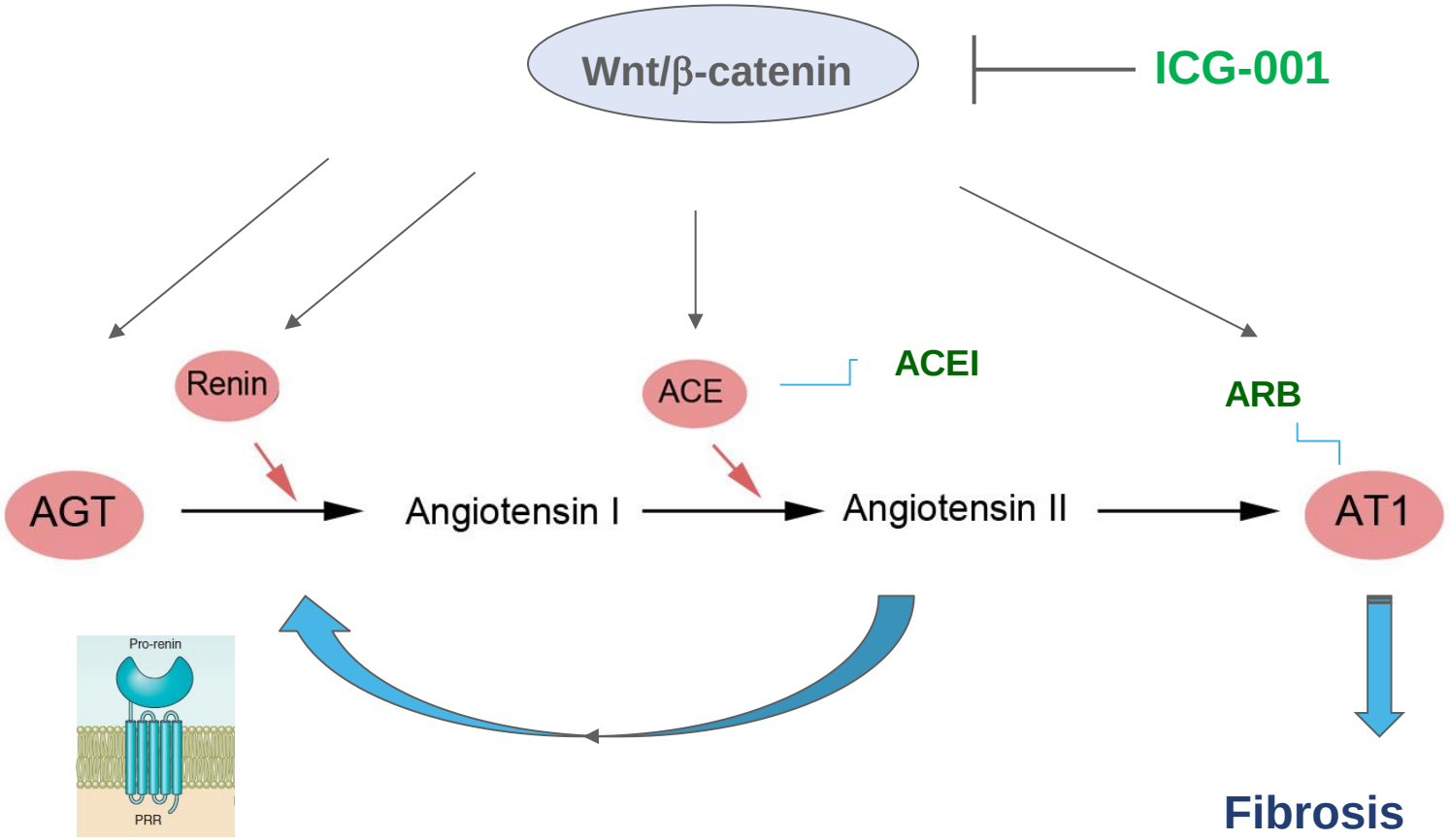
ICG-001, but not RAS blocker, completely inhibits RAS expression



Renin promotes renal fibrosis by Ang II-independent mechanism



Summary


Wnt/β-catenin
ICG-001
Renin
ACE
ACEI
ARB
AGT
Angiotensin I
Angiotensin II
AT1
Pro-renin
PRR
Fibrosis
Inflammation
Hypertension

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Dong Zhou

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