Fibrosis and anti-fibrotic therapy

Shougang Zhuang
Department of Medicine
Rhode Island Hospital
Brown University School of Medicine
USA

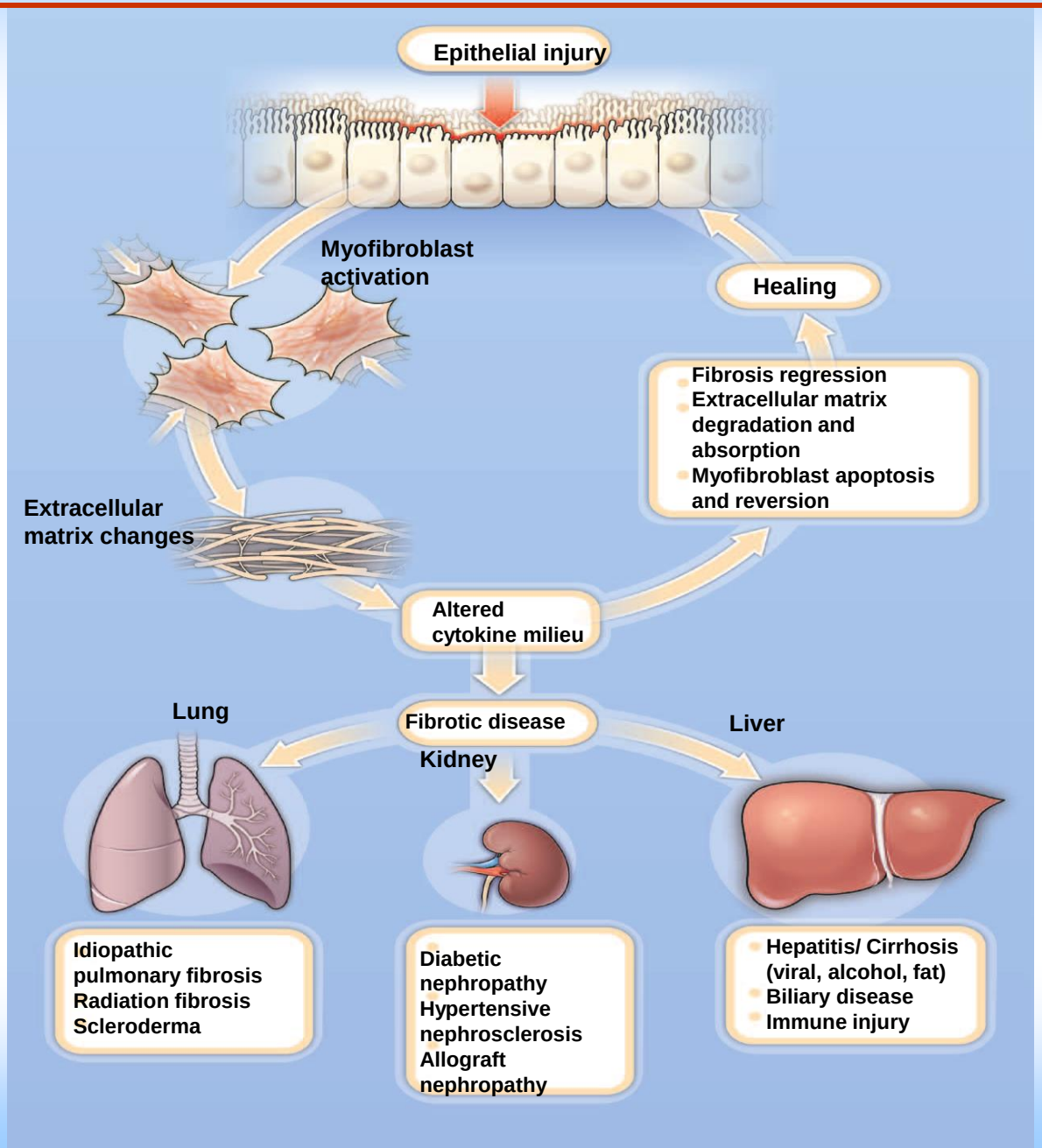
Department of Nephrology
Shanghai East Hospital
Tongji University School of Medicine
Shanghai, China

Fibrotic diseases

- Fibrotic diseases contributes to as much as 45% of deaths in the industrialized world
- Fibrotic diseases have been largely overlooked
- The pathogenesis of fibrosis is characterized by activation/proliferiaton of myofibroblasts and accumulation of ECM in response to injury

- Fibrotic diseases are becoming therapeutically tractable

Common events in fibrosis across tissues

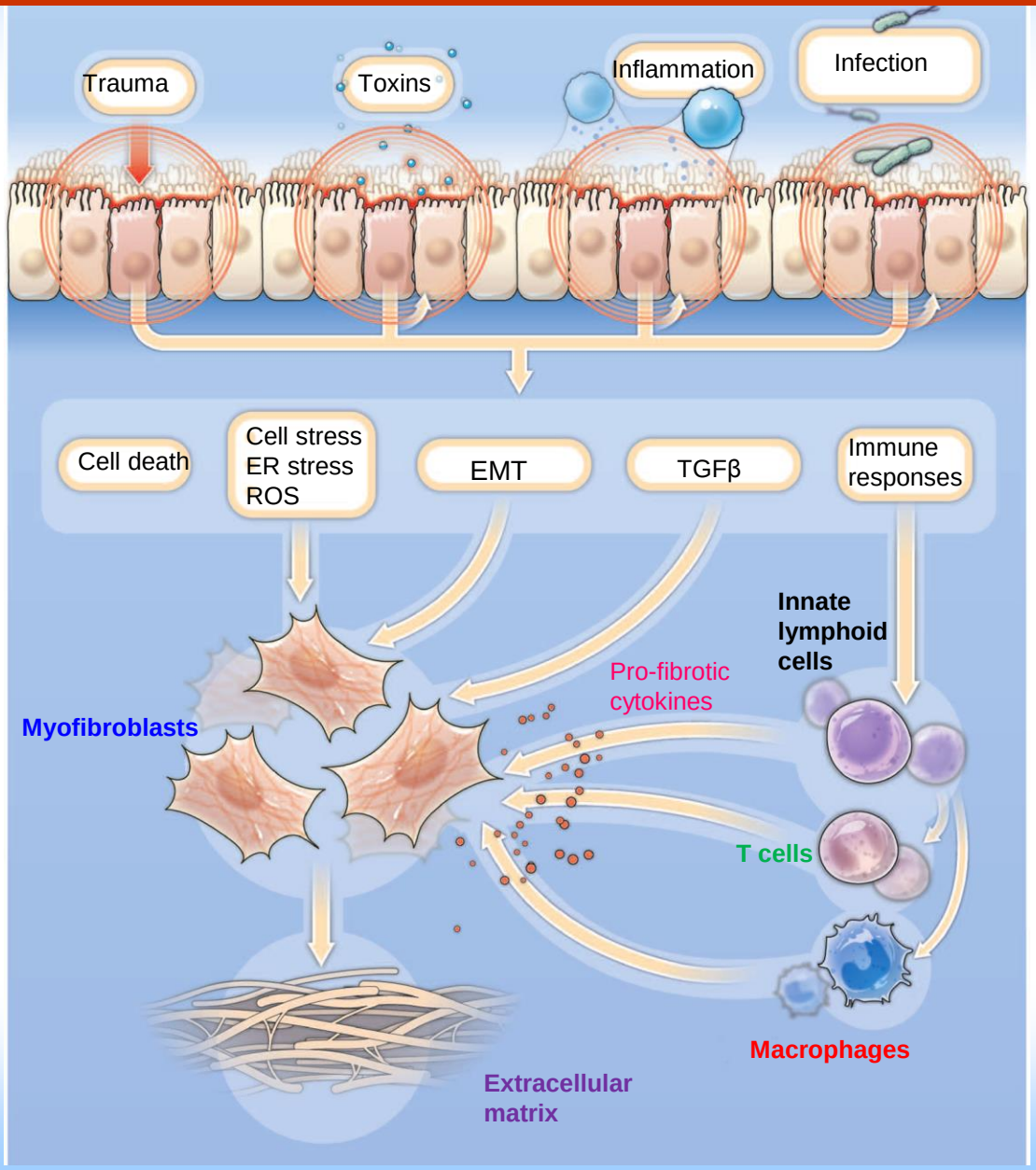


Core features shared by pathologic fibrosis among multiple organs

- Recurrent or persistent epithelial injury is a core element that both initiates and sustains progressive fibrosis

- Five responses to injury-induced functional or physical disruption of epithelial cells can provoke tissue fibrosis
  - Cell death
  - the dysregulation of metabolic pathways
  - Partial epithelial to-mesenchymal transition (EMT) via Twist- and Snail-driven cellular reprogramming
  - Interactions between integrins and TGFβ.
  - Initiate both innate and adaptive immune responses

Mechanisms by which epithelial injury can lead to organ fibrosis



Resolution and regression of fibrosis

- Induce proteases, especially matrix metalloproteinases (MMPs)
- Take up the cleaved matrix protein fragments by tissue phagocytes or fibroblasts
- Reduce inflammation by macrophage phagocytosis of apoptotic epithelial cells
- Induce and promote myofibroblast apoptosis
- Reverse myofibroblasts to a more quiescent phenotype
- Control sources of liver injury (i.e. antiviral therapies for viral hepatitis)

Prevention and treatment of CKD

	Rationale	Target population	Examples*
Reduction of the risk of CKD	Interventions for modifiable factors that can cause or increase susceptibility to kidney disease	All adults	Prevention, detection, and treatment of hypertension and diabetes
Early detection of CKD	Laboratory testing to detect presence of asymptomatic disease	Adults at increased risk of CKD (hypertension, diabetes, clinical CVD, family history of kidney failure, or age ≥60 years)	Urinary albumin-to-creatinine ratio as a marker of kidney damage, serum creatinine to estimate GFR
Identification of the clinical diagnosis (cause and pathology)	Specific therapy directed at the clinical diagnosis	All patients with CKD	See panel 1
Slowing the progression of CKD and of albuminuria	Non-specific therapies, irrespective of the cause of CKD	All patients with CKD (high priority in patients with high-risk CKD)	ACE inhibitors or ARBs for patients with albuminuria, low blood-pressure goal
Prevention of complications of decreased GFR: threats to patient safety	Avoiding toxic effects of drugs and drug-induced AKI	Patients with CKD stages 3–5	Drug dosing based on eGFR; avoiding NSAIDs, iodinated radiographic contrast, phosphate-based bowel preparation, gadolinium (CKD stages 4–5); prevention of contrast AKI with isotonic saline or bicarbonate
Prevention of complications of decreased GFR: uraemic complications	Therapy directed at altered pathophysiology	Patients with CKD stages 3–5 (more often in stages 4–5)	ESA and iron for anaemia; vitamin D and phosphate binders for CKD-MBD; appropriate energy intake for malnutrition; referral to nephrologists
Treatment of the nephrotic syndrome	Non-specific therapies, irrespective of the cause of CKD	Patients with urine ACR >2000 mg/g	ACE inhibitors or ARBs, restriction of dietary sodium, diuretics, statins, consider anticoagulation
Improvements in the outcomes of dialysis and transplantation	Preparation and timely initiation of kidney replacement therapy	Patients with CKD stages 4–5 (more often in stage 5)	Modality selection for dialysis; access placement for haemodialysis; recipient selection for transplantation; donor selection for transplantation; adequate dialysis dose; improved immunosuppression for transplantation; complications associated with decreased GFR and albuminuria after transplantation
Reduction of the risk of CVD	Treatment of CVD risk factors and clinical CVD	All patients with CKD (high priority in patients with high-risk CKD)	CKD as the highest risk group for blood pressure, lipids

For references see table 1, webappendix pp 1–10. CKD=chronic kidney disease. CVD=cardiovascular disease. GFR=glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. AKI=acute kidney injury. eGFR=estimated GFR. NSAID=non-steroidal anti-inflammatory drug. ESA=erythropoietin-stimulating agent. CKD-MBD=CKD-mineral and bone disorders. ACR=albumin-to-creatinine ratio. *References to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[9] if available, and to other guidelines and consensus statements if no KDIGO guideline is available.

Table 1: **Overview of strategies for prevention, detection, evaluation, and management to improve outcomes of chronic kidney disease in adults**

Potential therapeutic targetes in renal fibrosis (1)

Target group	Therapeutic targets and/or approach
Renin–angiotensin–aldosterone system	ACE *(ACEI)*, Ang II R 1 *(ARB)*, aldosterone *(aldosterone antagonists)*, renin *(renin inhibitors)*
ECM turnover	MMP-1, MMP-2, TIMPs-1, ADAM-19, ADAM-17, tissue transglutaminase, ILK, relaxin *(relaxin), trypsin+bromelain+rutosid, pirfenidone*
Cytokines	IL-1 *(IL-1 receptor antagonist)*, IL-4, IL-8, IL-10 *(anti-IL-10 Ab)*, IFN-γ *(IFN-γ)*, IFN-α*(IFN-α)*, TNF-α *(anti-TNF-α-Ab)*
Chemokines SLC/CCR7 *(chemokine*	MCP-1/CCR2, RANTES/CCR1, M-CSF, osteopontin, CX3CR1, *receptor antagonists)*
TGF-β signaling	TGF-β, Smad-7, Smad-3 (*halofuginone)*, Snail, Ski, SnoN, ALK5, BMP-7, CTGF
Growth factor receptors	PDGFR , VEGFR *(anti-VEGFR-Ab)*, EGFR *(anti-EGFR-Ab)*
Intracellular transduction cascades:	NF-κB *(curcumin)*, Rho/ROCK *(Rho inhibitors)*, p38 MAPK *(p38 inhibitors)*, JNK, PKC-β, PI3Kγ *(PI3Kγ inhibitors)*, Notch, *various tyrosin kinase inhibitors*
Various	stem cells, mast cells, B-cells, AGEs, AOPPs, PPARγ *(glitazones), vitamin D, paracalcitol, G2/M cell cycle, HDAC.*

Potential therapeutic targetes in renal fibrosis (2)

VEGFR	Nintedanib (BIBF1120)
FGFR	Sorafenib
Other intracellular pathways	
JAK2	TG 101209
Wnt	Dkk-1
Hedgehog	LDE223
Notch	DAPT
RhoA	Statins, GGT inhibitor
ROCK	Y27632, fasudil
MEK, ERK,JNK, Akt,	caveolin scaffolding domain (CSD)
JNK	CC-930
Transcription factors	
AP-1	T-5524
Fli-1	Macrolide antibiotics
Sp1	Intercalating agents
PPARγ	Rosiglitazone
Other mechanisms	
IL-13	Humanized monoclonal AB
IL-6 receptor	Tocilizumab
TLR	TLR inhibitors (E5564, TAK-242)
Nox4 (ROS)	GKT136901
ET-1	Bosentan, other ET receptor blockers
Matrix stiffness, collagen crosslinking	D-penicillamine, clostridial collagenase

Pirfenidone: Mechanism of action

- Pirfenidone has both anti-inflammatory and anti-fibrotic effects
- Its actions is associated with its inhibition of both production and activity of TGF-β1
- It has been studied in multiple models of CKD including glomerulosclerosis (remnant kidney, unilateral ureteral obstruction, FGS/Kist mouse, diabetes (streptozotocin rats) and db/db mice)

Pirfenidone: Clinical efficacy

- A single-center, open-label pilot study to evaluate if pirfenidone can slow the GFR decline in adult patients with biopsy-proven idiopathic and post-adaptive FSGS
- 21 patients were enrolled, eGFR of 26±9.4 ml/min/1.73m^2 and median baseline proteinuria of 2.8 g/d
- 800 mg, three times daily for 12 months
- The monthly eGFR decline rate: from −0.61 to −0.45 ml/min/1.73m^2 , no effect on proteinuria
- Pirfenidone slows renal function decline in patients with FSGS
- The lack of placebo control, a larger, randomized, placebo-controlled trial is needed

Cho et al., Clin J Am Soc Nephrol; 2(5):906-13

Pirfenidone for diabetic nephropathy

- A randomized, double-blind, placebo-controlled study in 77 subjects with diabetic nephropathy
- Elevated albuminuria and reduced estimated GFR (eGFR) (20 to 75 ml/min per 1.73 m^2)
- 26 subjects assigned to placebo, 26 to pirfenidone at 1200 mg/d, and 25 to pirfenidone at 2400 mg/d.
- eGFR was increased in the pirfenidone 1200-mg/d group (+3.3 $\pm$ 8.5 ml/min per 1.73 m^2) whereas the mean eGFR decreased in the placebo group (-2.2 $\pm$ 4.8 ml/min per 1.73 m
- This study suggests that pirfenidone is a promising agent for individuals with overt diabetic nephropathy

Sharma et al., J Am Soc Nephrol. 2011;22(6):1144-51

BARDOXOLONE: Mechanism of Action

- Bardoxolone methyl induces the transcription factor Nrf2, which increases the production of antioxidant and reductive molecules (NQO1, HO-1, SOD1, γ-GCS) and inhibits the production of reactive oxygen species (ROS) and other pro-oxidant and pro-inflammatory molecules (iNOS, COX2, TNF-α).

- Induction of Nrf2 also reduces the pro-inflammatory activity of the IKKβ/NF-κB complex. Through these mechanisms, bardoxolone methyl reverts cells to a non-inflammatory state and thereby limits tissue damage to the host.

Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease

- 2185 patients with type 2 diabetes mellitus and stage 4 CKD
- eGFR15 to <30 ml per minute per 1.73 m(2) to bardoxolone methyl, at a daily dose of 20 mg, or placebo
- A total of 69 of 1088 patients (6%) assigned to bardoxolone methyl and 69 of 1097 (6%) assigned to placebo
- The trial was terminated due to a higher rate of cardiovascular events with bardoxolone methyl
- Bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes
- Bardoxolone has been approved to treat idiopathic pulmonary fibrosis by the FDA

de Zeeuw et al., N Engl J Med. 2013;369(26):2492-503

Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis (N Engl J Med. 2014 May 29;370(22):2071-82)

- **Nintedanib (**BIBF 1120, Ingelheim) is a small-molecule, broadly active tyrosine kinase inhibitor that inhibits PDGFR, FGFR, and VEGFR
- A phase 3 trials, 52-week, randomized, double-blind to evaluate the efficacy and safety of BIBF 1120 in patients with idiopathic pulmonary fibrosis
- A total of 1066 patients, 150 mg of BIBF 1120, twice daily, as compared with placebo
- The primary end point is the annual rate of decline in forced vital capacity (FVC)
- The decline in FVC was reduced in BIBF 1120–treated group
- BIBF 1120 is able to slow disease progression, leading to a historic approval by the FDA

Potential therapeutic targtes in renal fibrosis

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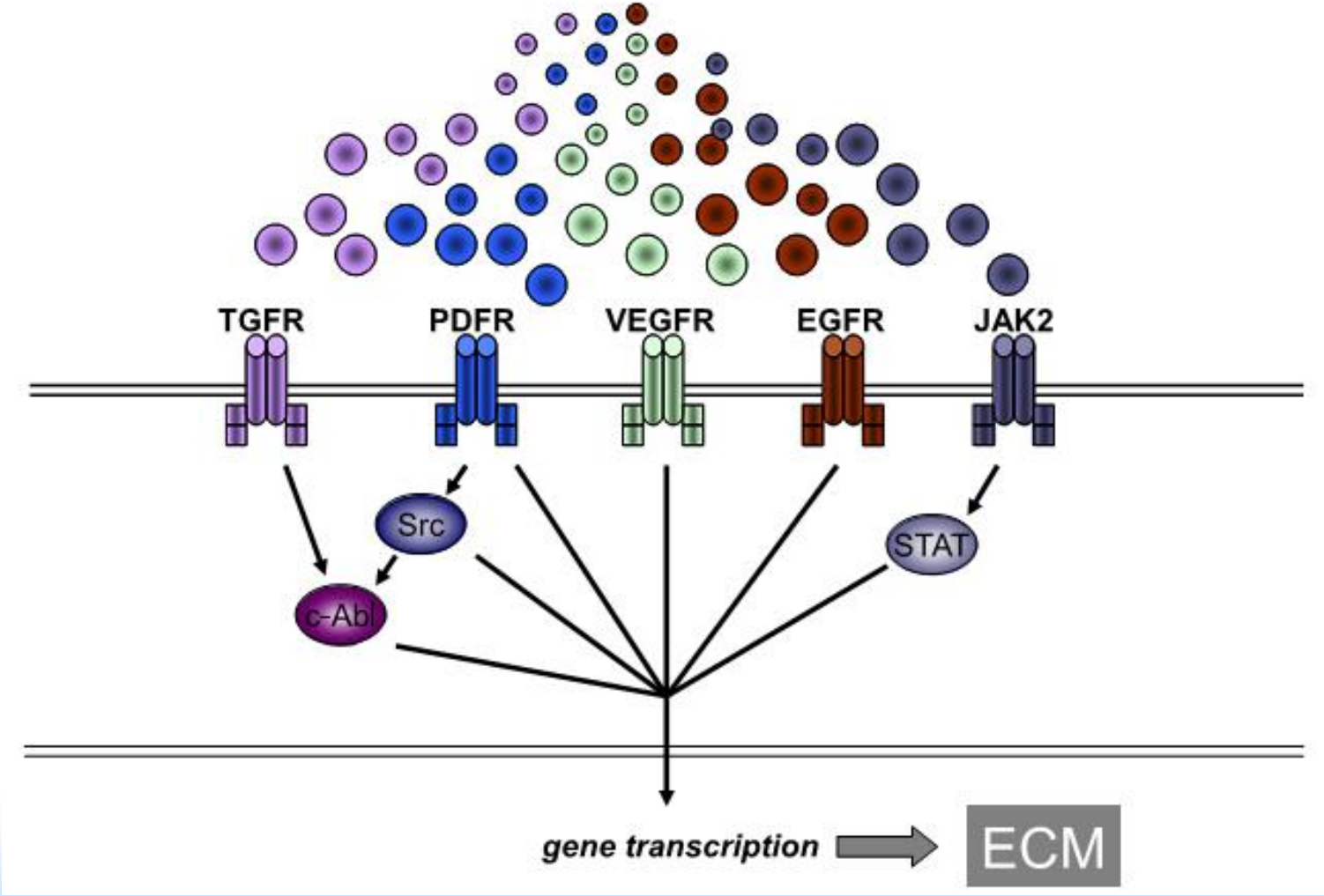
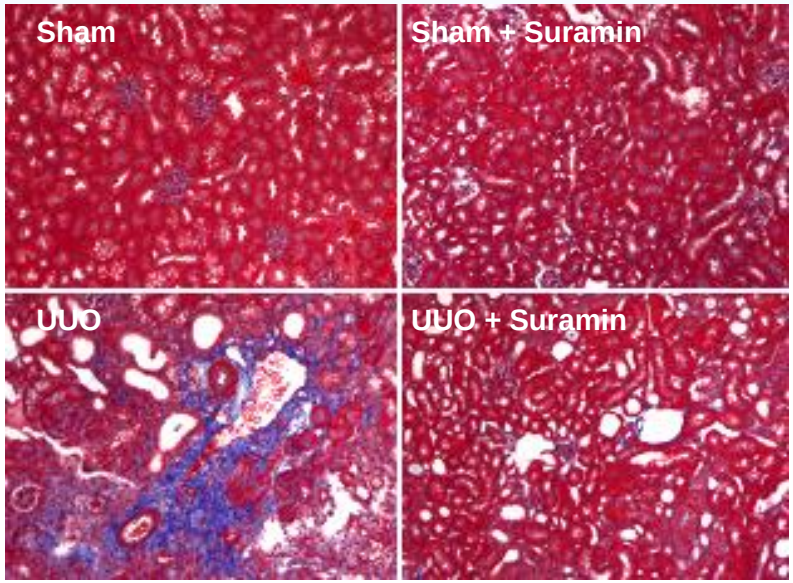
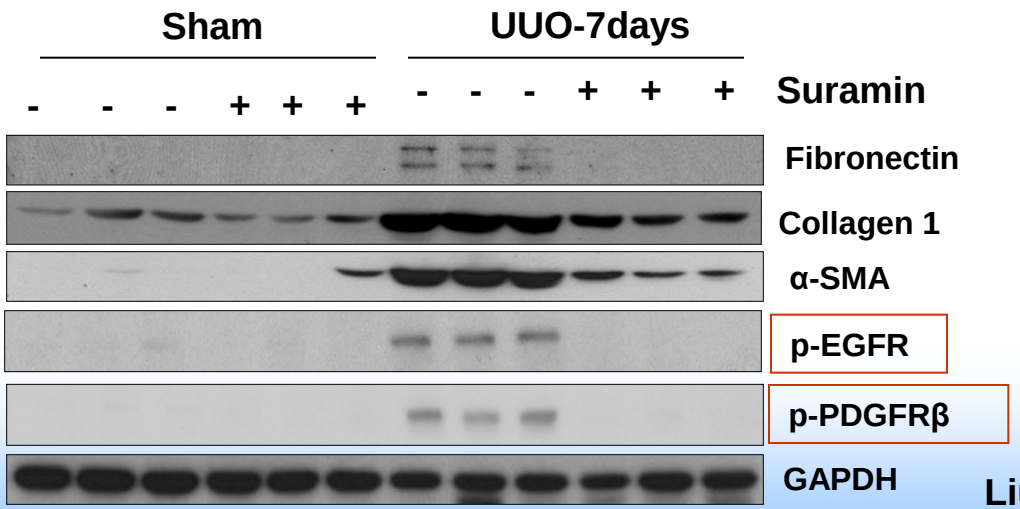
Growth factor receptors mediates renal fibrosis

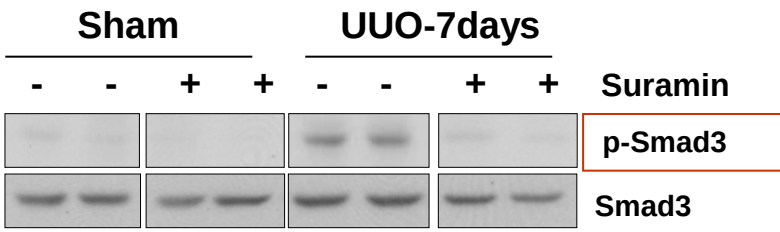


Suramin attenuates renal fibrosis in UUO



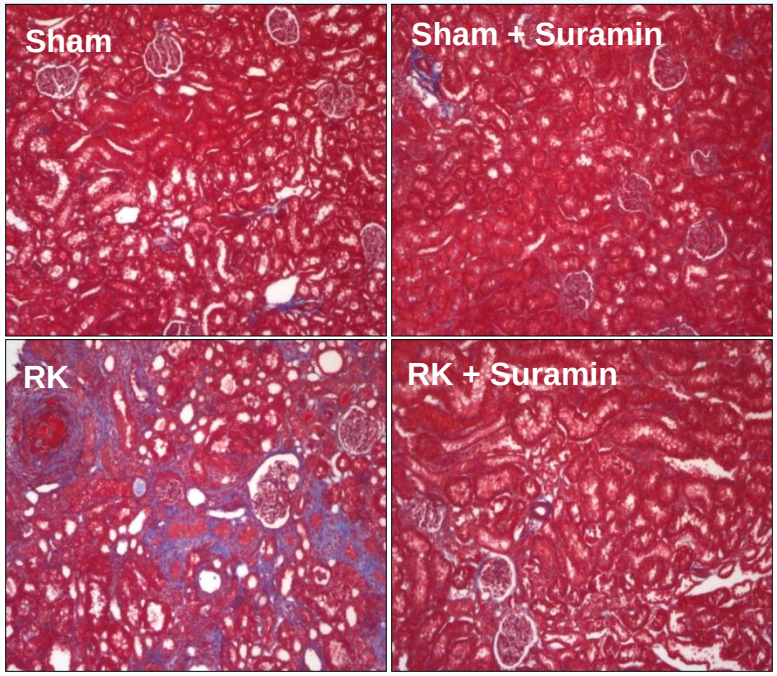
Suramin:
- **A FDA approved drug for prostate cancer**
- **Inhibits the interaction of multiple cytokines/growth factors with their receptors**



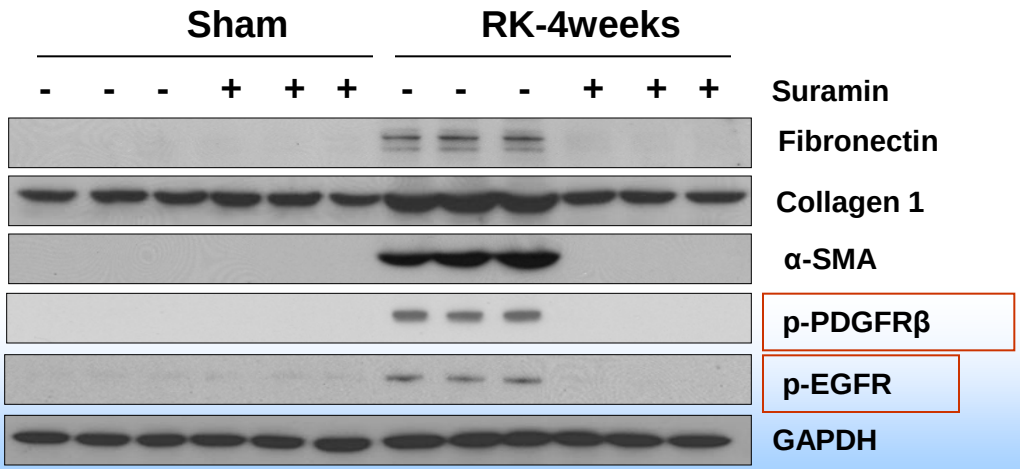


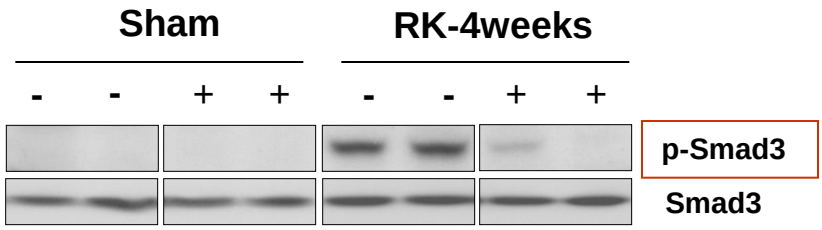
Liu et al., *J Am Soc Nephrol.* 2011;22:1064-75

Suramin inhibits renal fibrosis in remnant kidney



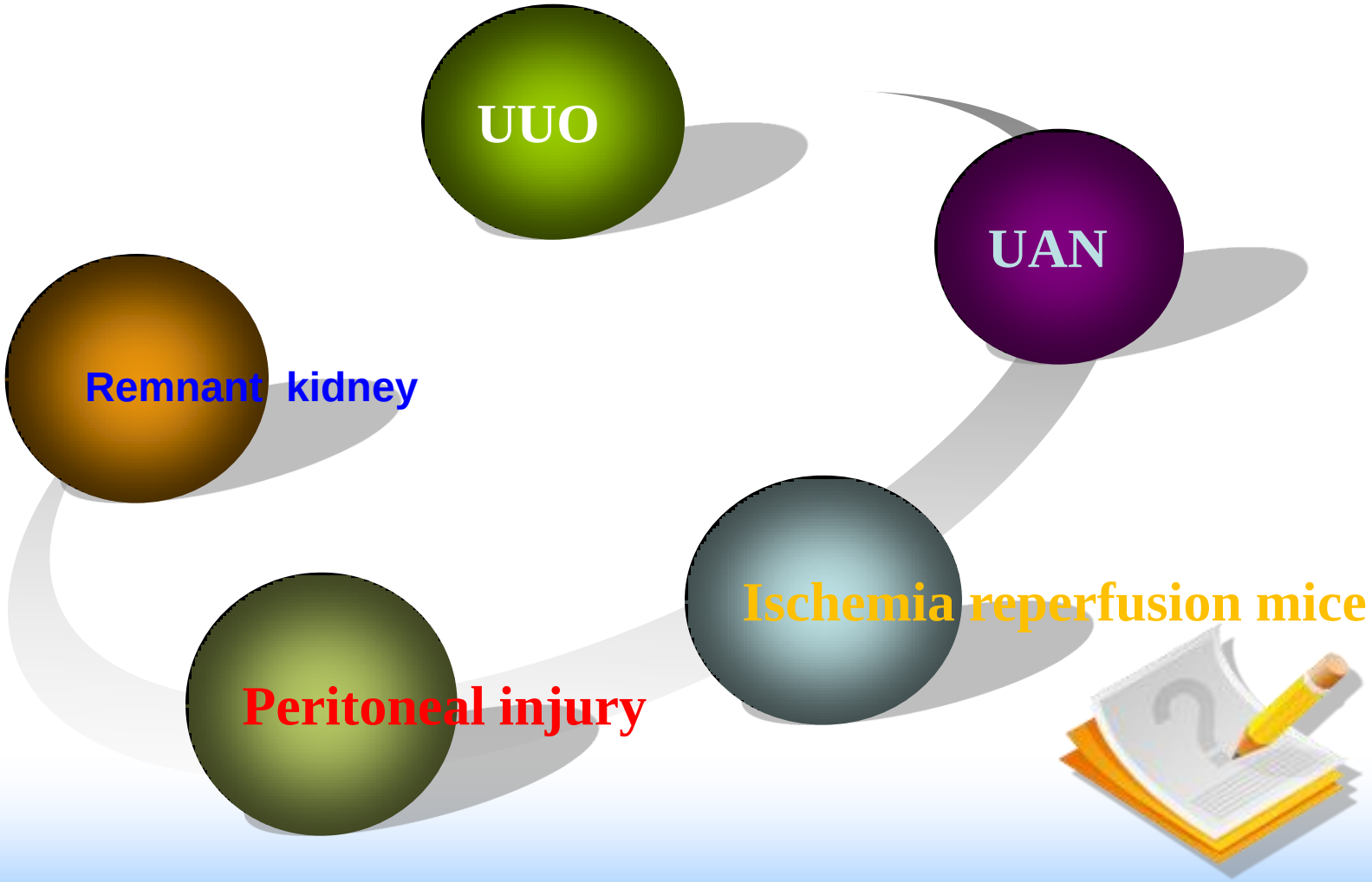
RK------Remnant kidney





Liu et al., *J Am Soc Nephrol.* 2011;22:1064-75

Suramin attenuates renal fibrosis in a variety of animal models



J Am Soc Nephrol. Mar 18, E public., 2015

BASIC RESEARCH www.jasn.org

EGF Receptor Inhibition Alleviates Hyperuricemic Nephropathy

Na Liu,* Li Wang,* Tao Yang,† Chongxiang Xiong,‡ Liuqing Xu,* Yingfeng Shi,* Wenfang Bao,* Y. Eugene Chin,§ Shi-Bin Cheng,‖ Haidong Yan,* Andong Qiu,¶ and Shougang Zhuang*‡

ABSTRACT

Hyperuricemia is an independent risk factor for CKD and contributes to kidney fibrosis. In this study, we investigated the effect of EGF receptor (EGFR) inhibition on the development of hyperuricemic nephropathy (HN) and the mechanisms involved. In a rat model of HN induced by feeding a mixture of adenine and potassium oxonate, increased EGFR phosphorylation and severe glomerular sclerosis and renal interstitial fibrosis were evident, accompanied by renal dysfunction and increased urine microalbumin excretion. Administration of gefitinib, a highly selective EGFR inhibitor, prevented renal dysfunction, reduced urine microalbumin, and inhibited activation of renal interstitial fibroblasts and expression of extracellular proteins. Gefitinib treatment also inhibited hyperuricemia-induced activation of the TGF-β1 and NF-κB signaling pathways and expression of multiple profibrogenic cytokines/chemokines in the kidney. Furthermore, gefitinib treatment suppressed xanthine oxidase activity, which mediates uric acid production, and preserved expression of organic anion transporters 1 and 3, which promotes uric acid excretion in the kidney of hyperuricemic rats. Thus, blocking EGFR can attenuate development of HN *via* suppression of TGF-β1 signaling and inflammation and promotion of the molecular processes that reduce uric acid accumulation in the body.

J Am Soc Nephrol 26: ●●●–●●●, 2015. doi: 10.1681/ASN.2014080793

- Liu N, Guo JK, Pang M, Tolbert E, Ponnusamy M, Gong R, Bayliss G, Dworkin LD, Yan H, **Zhuang S.** Genetic or pharmacologic blockade of EGFR inhibits renal fibrosis. *J Am Soc Nephrol.* 2012 May;23(5):854-67.

- Wang L, Liu N, Xiong C, Xu L, Shi Y, Qiu A, Zang X, Mao H and **Zhuang S**. Inhibition of EGF Receptor Blocks the Development and Progression of Peritoneal Fibrosis. *Am Soc Nephrol. (In press)*

- Tang J, Liu N, Tolbert E, Ponnusamy M, Ma L, Gong R, Bayliss G, Yan H, **Zhuang S.** Sustained activation of EGFR triggers renal fibrogenesis after acute kidney injury. *Am J Pathol.* 2013 Jul;183(1):160-72

- Tang J, Liu N, **Zhuang S.** Role of epidermal growth factor receptor in acute and chronic kidney injury. **Kidney Int.** 2013 May;83(5):804-10

- **Zhuang S**, Liu N. EGFR signaling in renal fibrosis. *Kidney Int Suppl* . 2014 Nov;4(1):70-74.

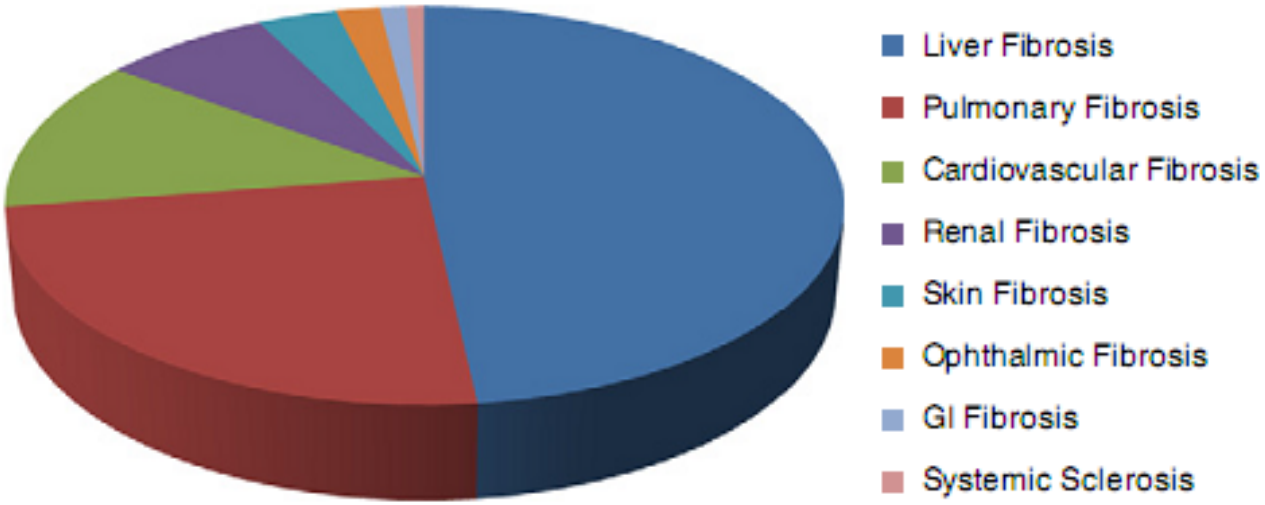
Clinical trials in CKD

- **CKD active clinic trials: 3122**
- **Questions: Lack of approved surrogate endpoints for kidney disease progression**

  old: doubling of the serum creatinine level

  2012 FDA and the National Kidney Foundation: 30-40% decline in eGFR

Current anti-fibrotic clinical trials

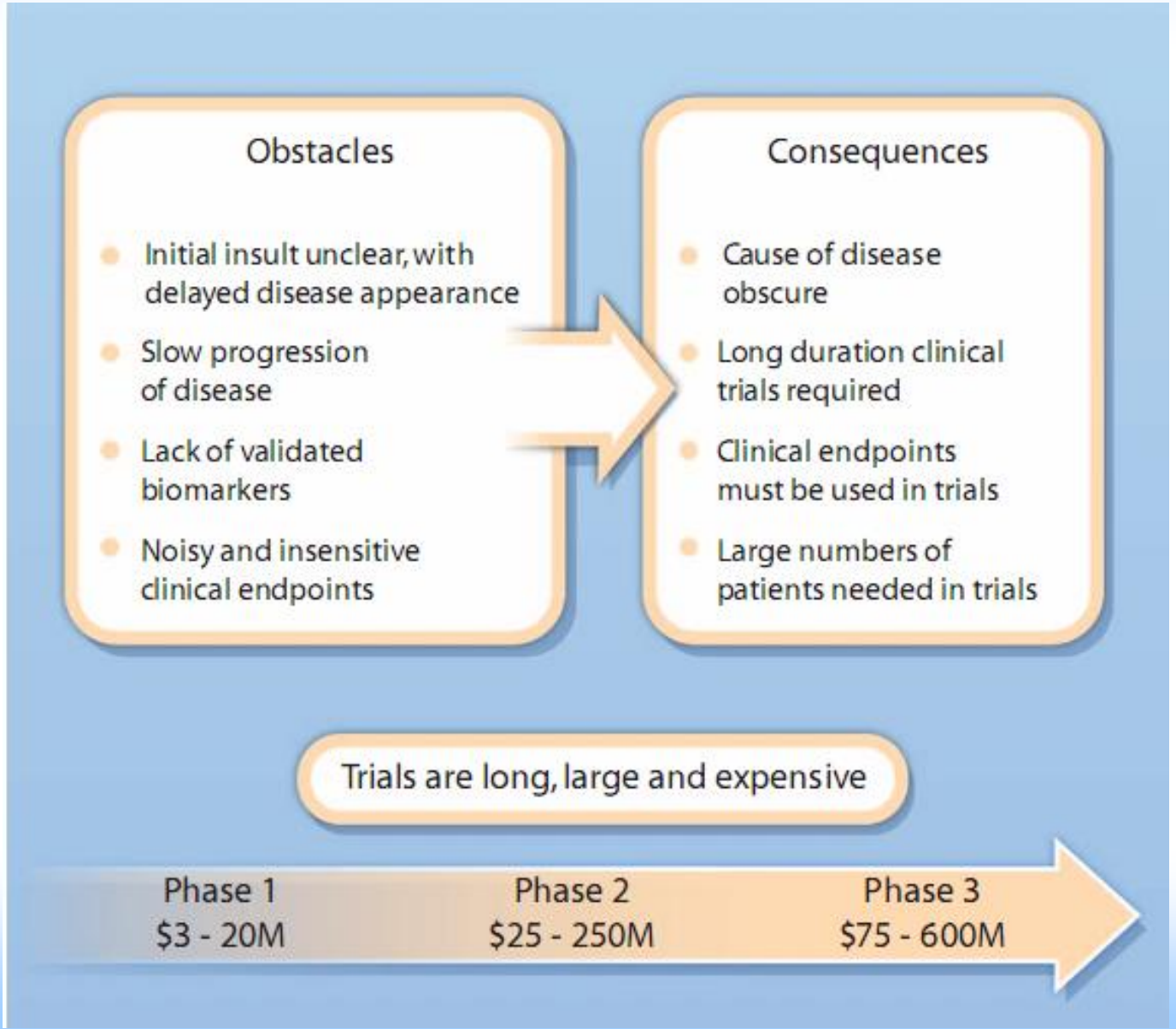


	Liver Fibrosis	123	48.24
	Pulmonary Fibrosis	62	24.31
	Cardiovascular Fibrosis	32	12.55
→	Renal Fibrosis	19	7.45
	Skin Fibrosis	9	3.53
	Ophthalmic Fibrosis	5	1.96
	GI Fibrosis	3	1.18
	Systemic Sclerosis	2	0.78
		255	100.00

Some clinical trials for treatment of CKD

- GC1008 (Genzyme) is a humanized antibody that binds and blocks the function of TGFβ1, -2, and -3
- LY2382770 (Lilly) is a humanized antibody that selectively binds and blocks the TGFβ1 cytokine
- STX-100 (Biogen Idec) is a humanized antiavb6 antibody
- BMS-986202 (Bristol-Myers Squibb) is a small-molecule antagonist of the LPA1 receptor
- GS-6624 (Gilead) is a noncompetitive allosteric antibody inhibitor of LoxL2

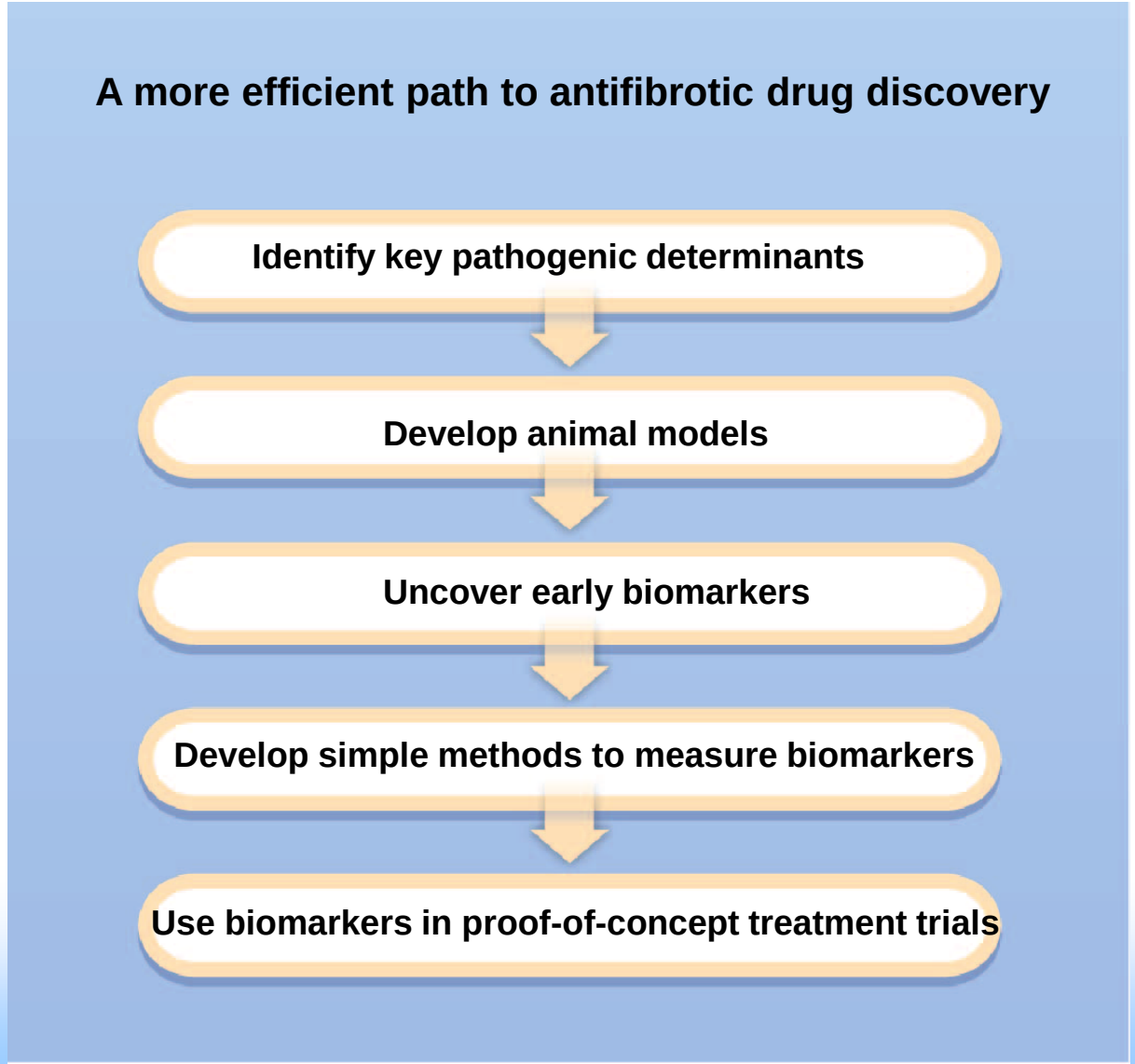
Obstacles to translation in developing antifibrotics



Principles for designing anti-fbrotic therapies

- Avoid targeting the conserved, or core, pathways of fibrosis for therapy
- Pinpoint targets that are unique to diseased tissue or are only expressed in a specific organ (i.e. PDGFβ)
- Fibrosis-specific targets confined to fibrogenic cells in injured tissues
- Cell surface molecules are appealing targets because of their accessibility to therapeutic antagonists

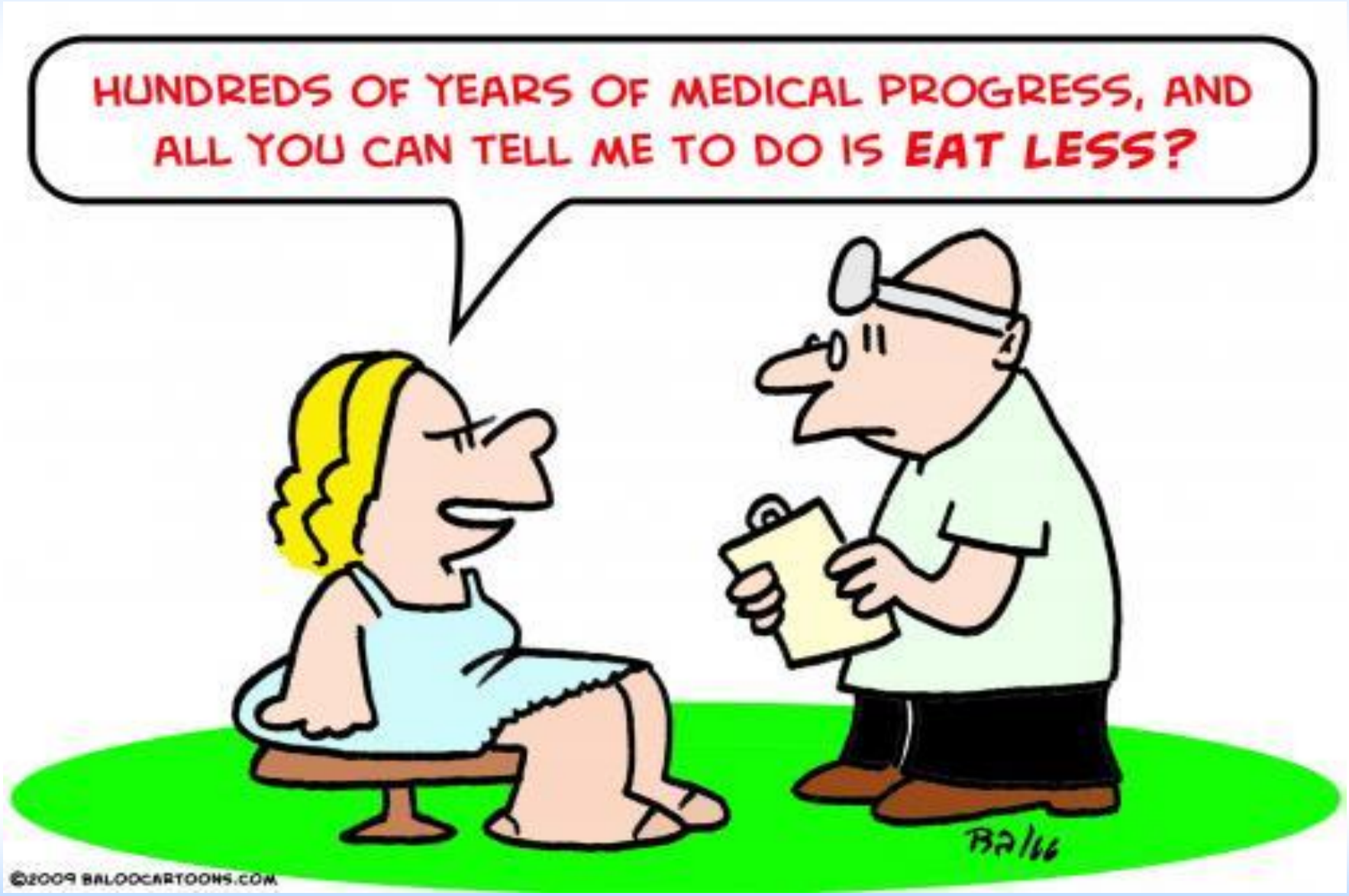
Narrowing the translational gap for antifibrotic therapy development



Future directions

- We need more insight into both shared and unique molecular pathways that drive fibrotic disease in various organs
- We need more clarity on guidelines for proper diagnosis of fibrotic diseases and a clearer understanding of rates of disease progression and how to monitor these changes
- We need to test therapeutic targets for which there is strong supporting scientific rationale in well-designed clinical trials with meaningful biomarker and functional endpoints

We need newer and better



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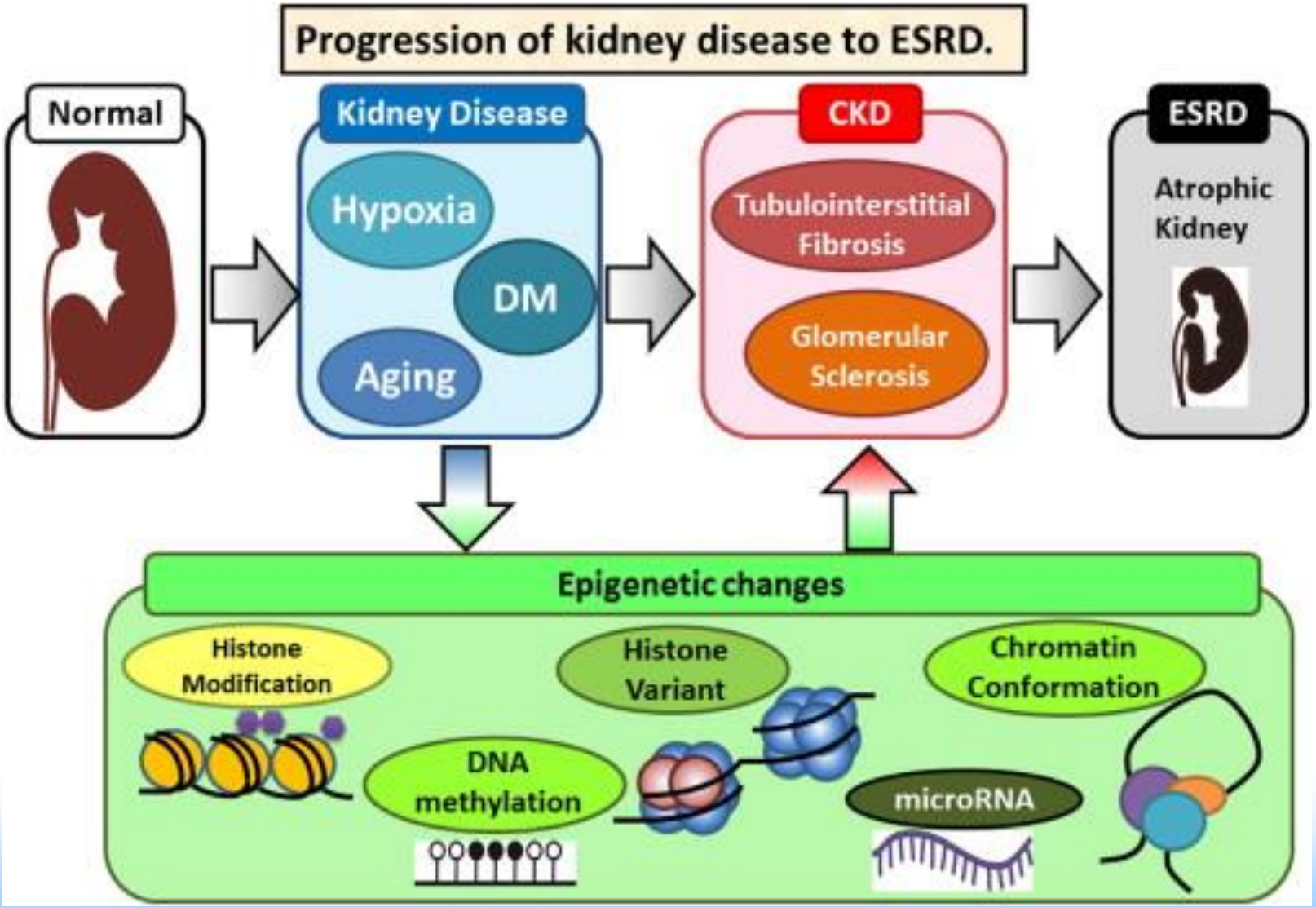
Epigenetic regulation is associated with progression of CKD



Epigenetic therapies for renal fibrosis

- **Noh…Lee et al.,** Histone deacetylase-2 is a key regulator of diabetes- and transforming growth factor-beta1-induced renal injury. Am J Physiol Renal Physiol.;297(3):F729-39, Sep, 2009

- **Pang …Zhuang et al**. Inhibition of histone deacetylase activity attenuates renal fibroblast activation and interstitial fibrosis in obstructive nephropathy. Am J Physiol Renal Physiol. 297(4):F996-F1005, Oct. 2009

- **Bechtel…Zeisberg et al:** Methylation determines fibroblast activation and fibrogenesis in the kidney. Nat Med 16: 544–550, 2010

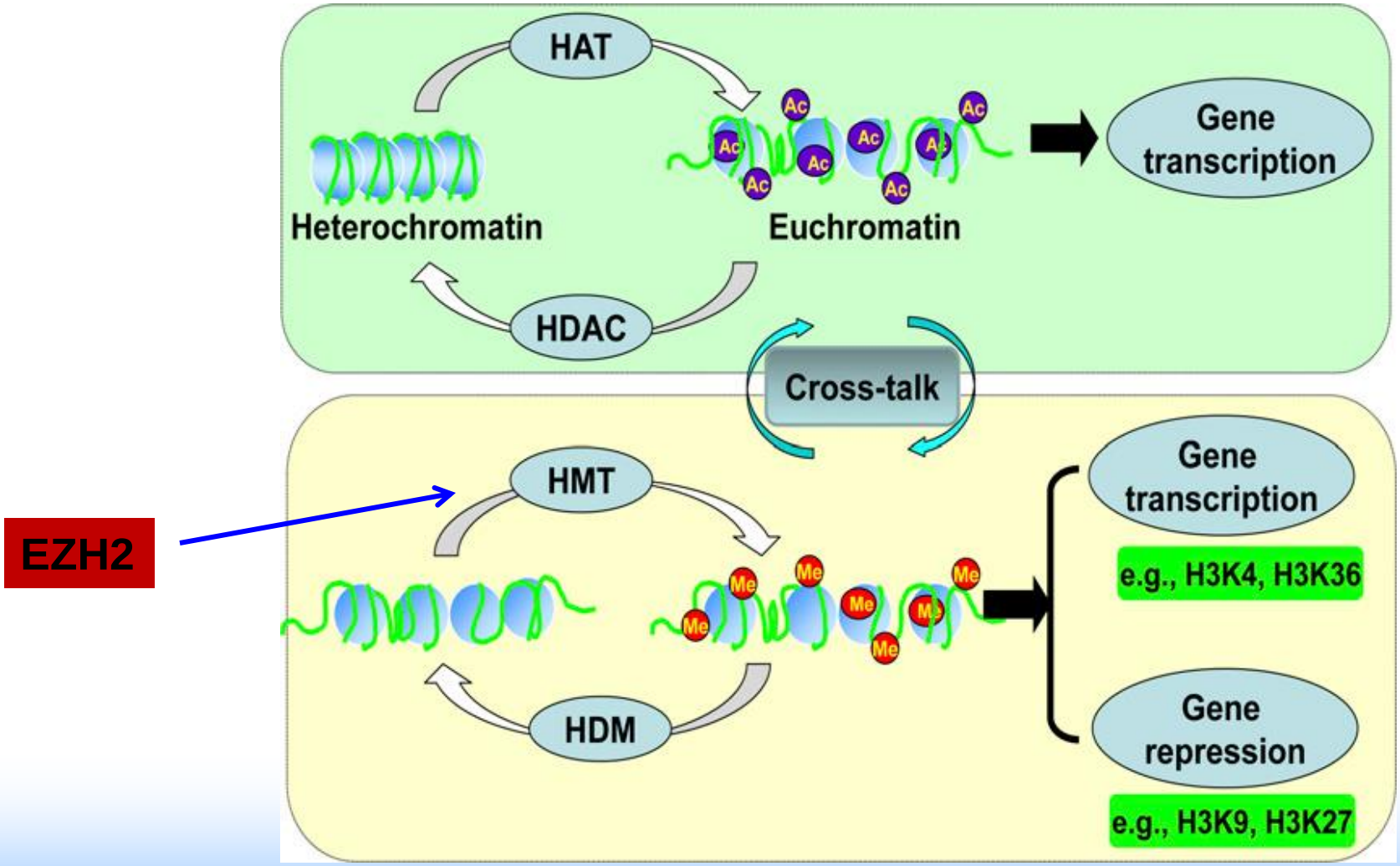
- **Irifuku …Masaki et al**., Inhibition of H3K9 histone methyltransferase G9a attenuates renal fibrosis and retains klotho expression. Kidney Int. 2015 Oct 7. doi: 10.1038/ki.2015.291

- **Zhou… Zhuang et al., Targeting EZH2 Methyltransferase Attenuates Renal Fibrosis.** J Am Soc Nephrol. (JASN，in press)

What is EZH2?

- EZH2 (Enhancer of Zeste Homolog 2) is a methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3)
- H3K27me3 is a transcriptionally repressive epigenetic marker
- H3K27me3 has been associated with suppression of multiple tumor suppressor genes
- EZH2 is overexpressed in many aggressive tumors with poor outcomes

Regulation and function of histone modifications



Epigenetic drugs in clinical applications and current research status

Table 1 Selected Epigenetic Drugs

Drug	Compound	Study Phase
DNMT inhibitors	Azacitidine (Vidaza)	US FDA–approved in MDS
	Decitabine (Dacogen)	US FDA–approved in MDS
	S110	Phase I
	CP-4200 (elaidic azacytidine)	Preclinical
	Nanaomycin A	Preclinical
HDAC inhibitors	Vorinostat (Zolinza)	US FDA–approved in CTCL
	Romidepsin (Istodax)	US FDA–approved in CTCL
	Panobinostat	Phase II
	Belinostat	Phase I/II
	Valproic acid	Phase II
	Belinostat	Phase II/III
HMT inhibitors	Deazaneoplanocin A (DZNep)	Preclinical
	Quinazoline derivatives	Preclinical
	Ellagic Acid	Preclinical
Histone demethylase inhibitors	Polyamine analogues	Preclinical
	Hydroxamate analogues	Preclinical
HAT inhibitors	Spermidinyl-CoA derivatives	Preclinical
	Hydrazinocurcumin	Preclinical
	Pyrazolone-containing small molecules	Preclinical

CoA = coenzyme A; CTCL = cutaneous T-cell lymphoma; DNMT = DNA methyltransferase; HAT = histone acetyltransferase; HDAC = histone deacetylase; HMT = histone methyltransferase; MDS = myelodysplastic syndrome.

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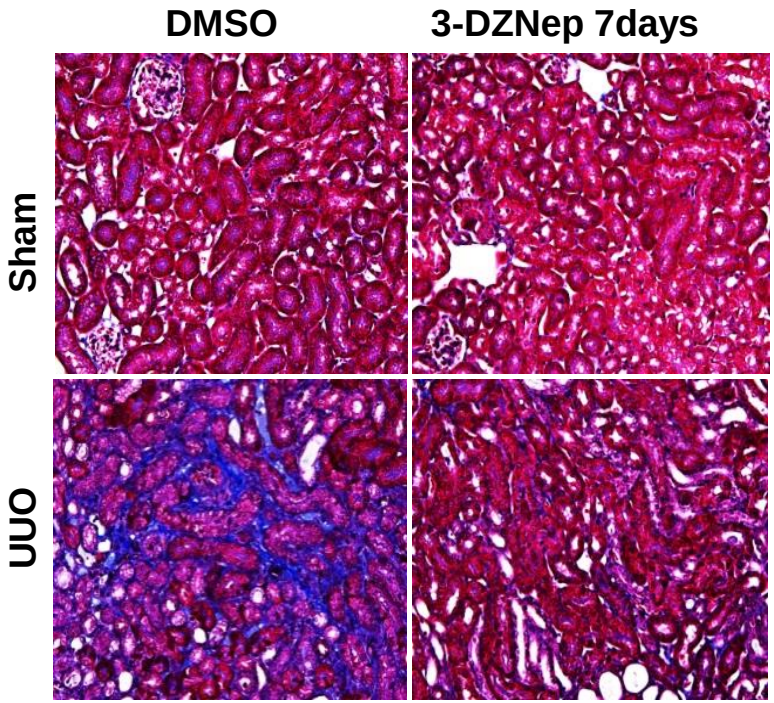
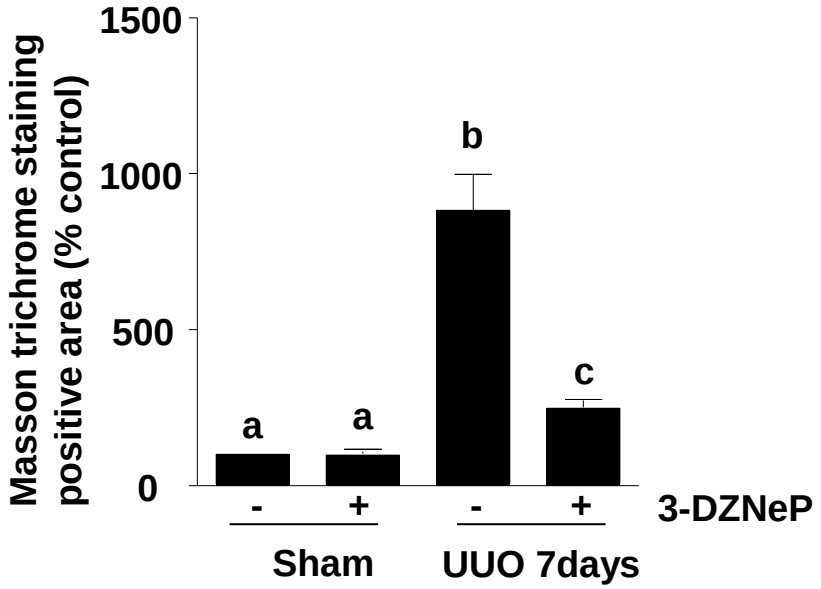
Our experiments

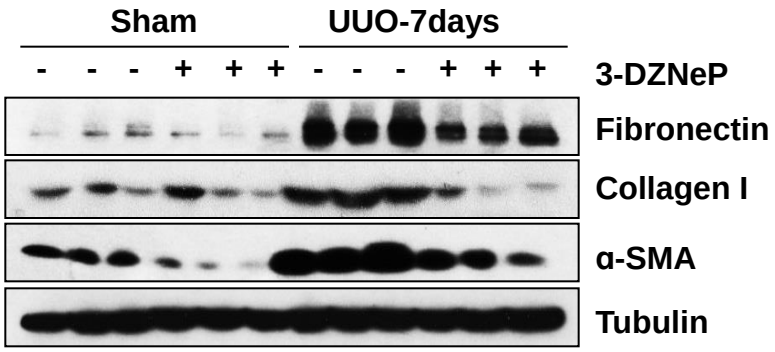
3-DZNeP attenuates development of renal fibrosis in obstructed kidneys

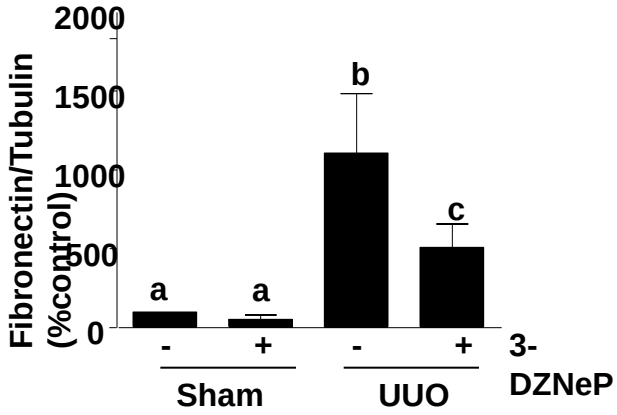


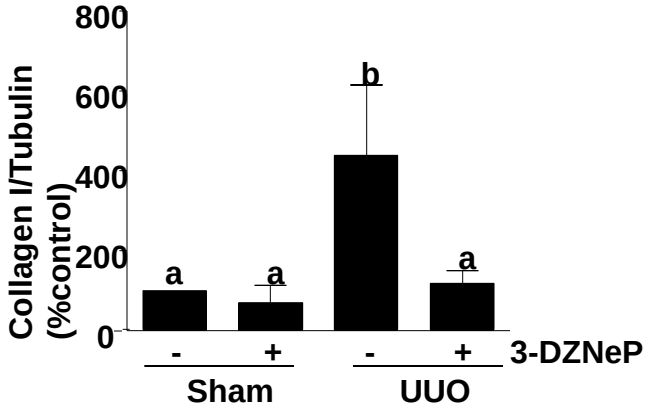


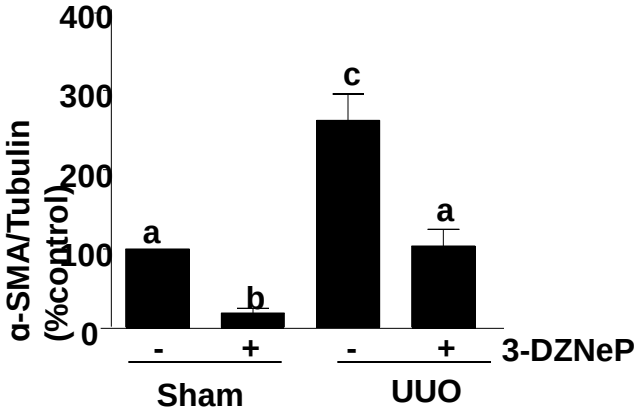
Zhou et al, JASN, in press

Blocking EZH2 with 3-DZNeP attenuates deposition of ECM proteins in obstructed kidneys









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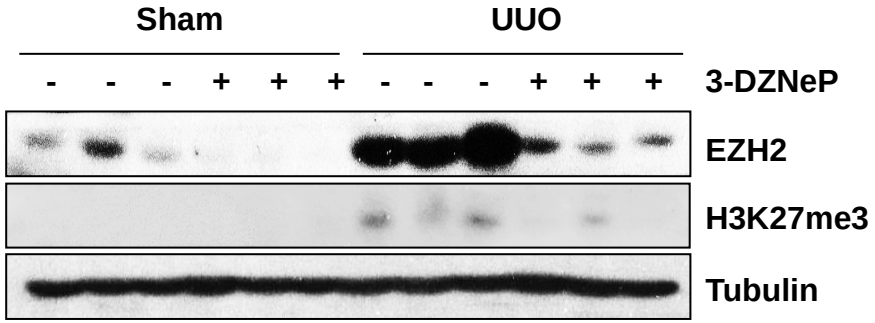
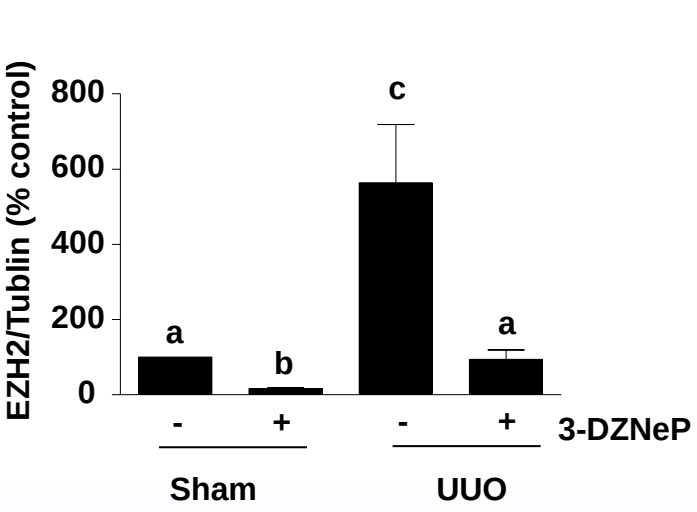
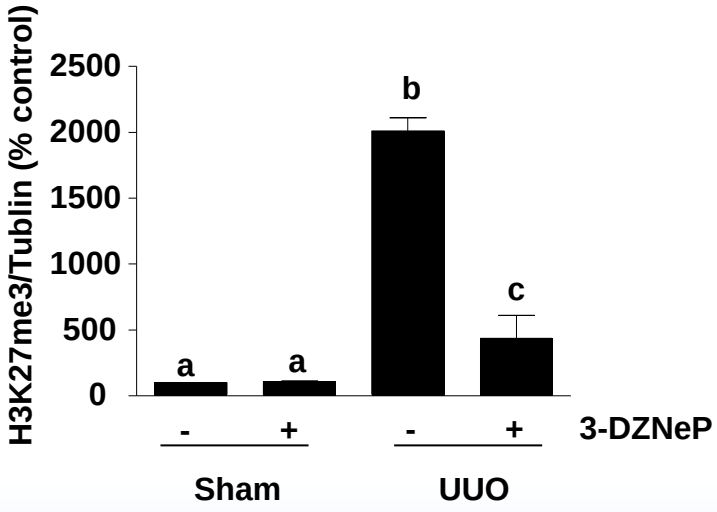
3-DZNep treatment induces degradation of EZH2 and histone demethylation in obstructed kidney







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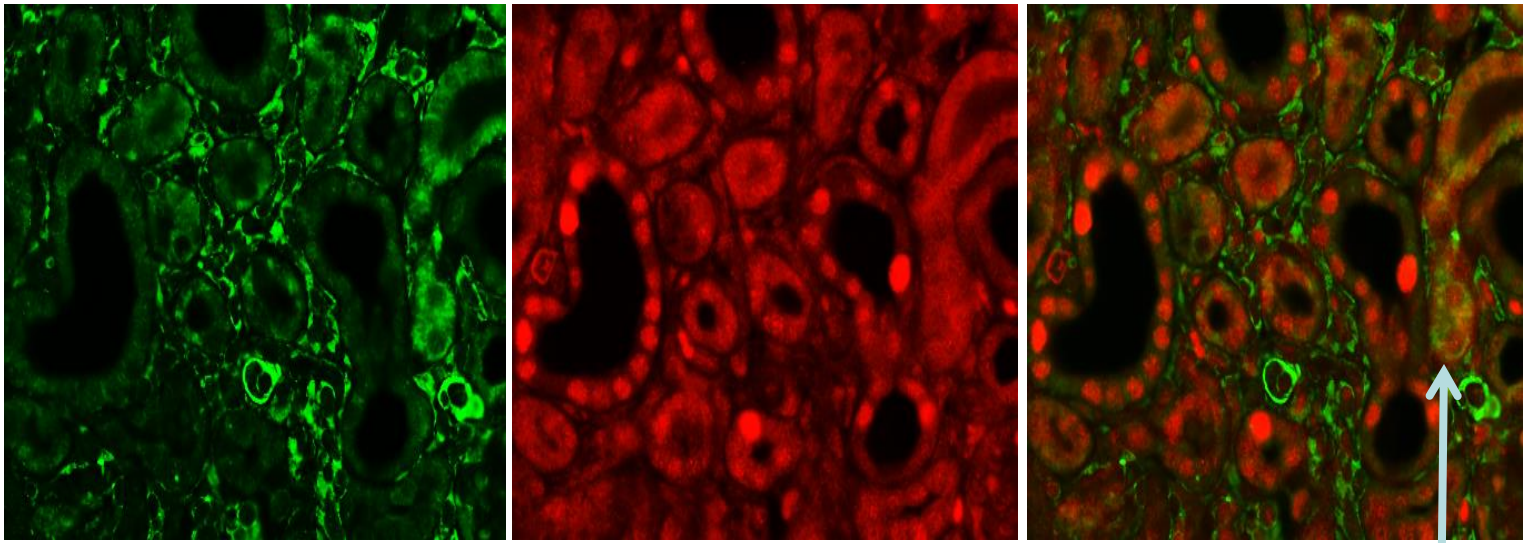
EZH2 在UUO损伤肾脏成纤维细胞和小管上皮细胞的表达



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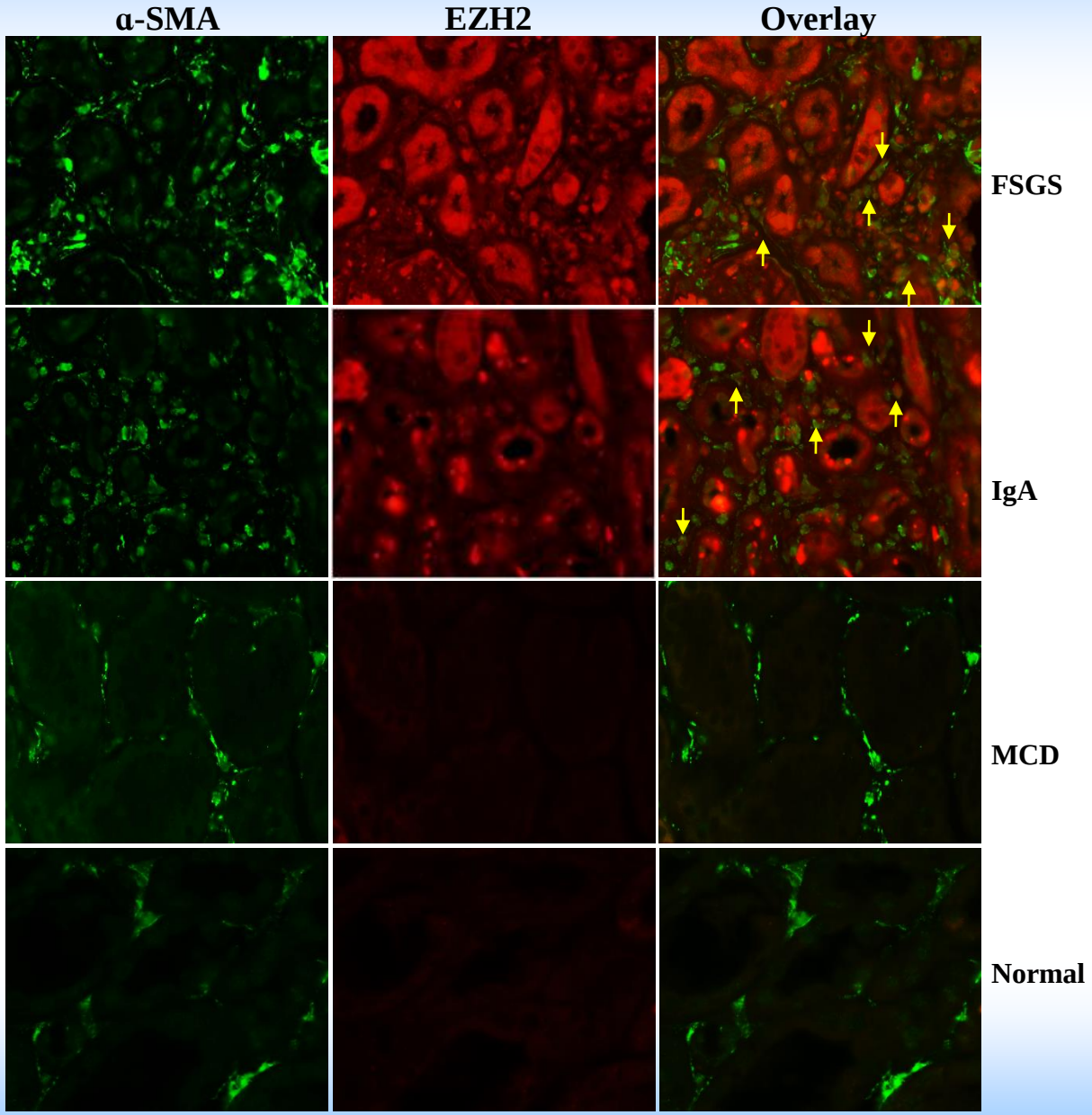
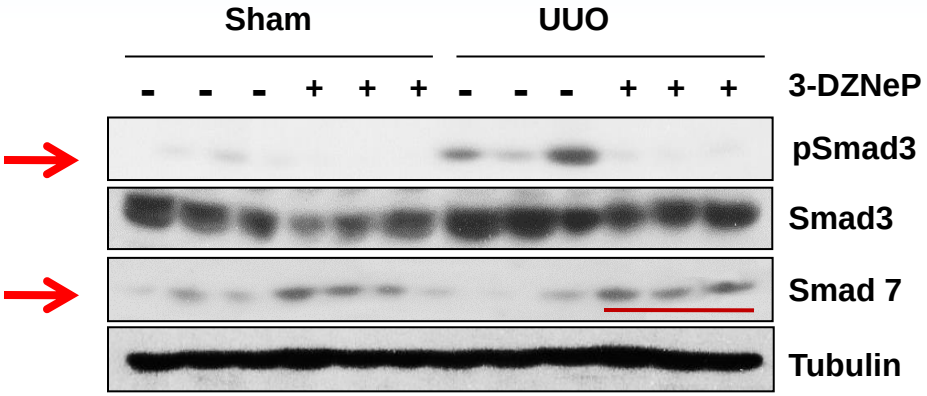
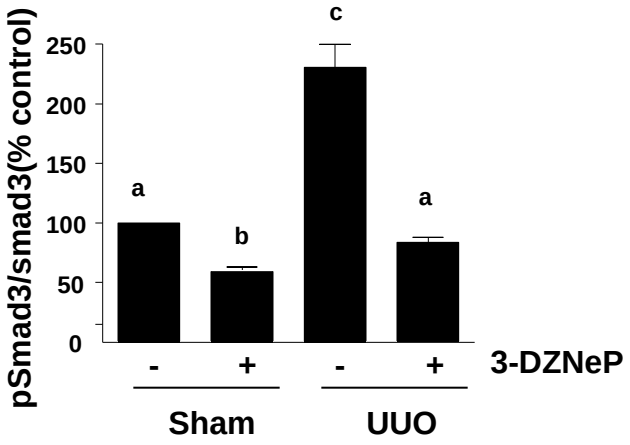
Expression of EZH2 in human kidneys

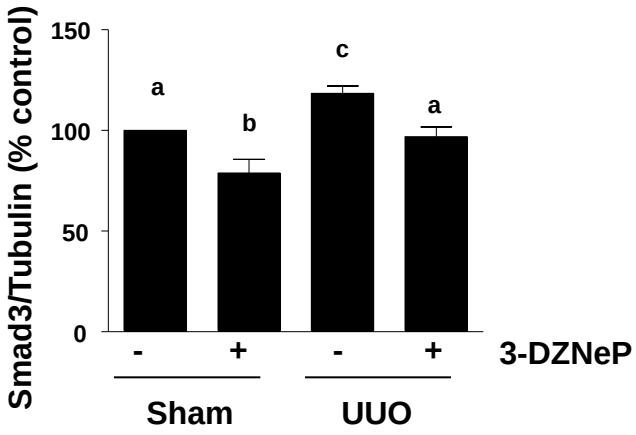


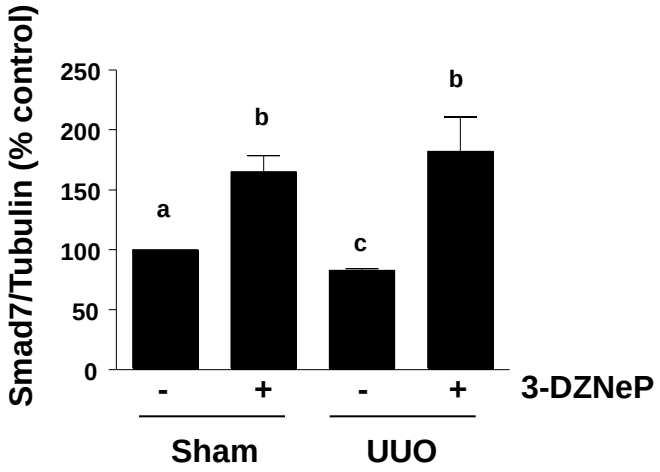
Human kidneys (600X)

Blocking EZH2 suppresses Smad-3 activation, but enhances Smad-7 expression in renal interstitial fibroblasts









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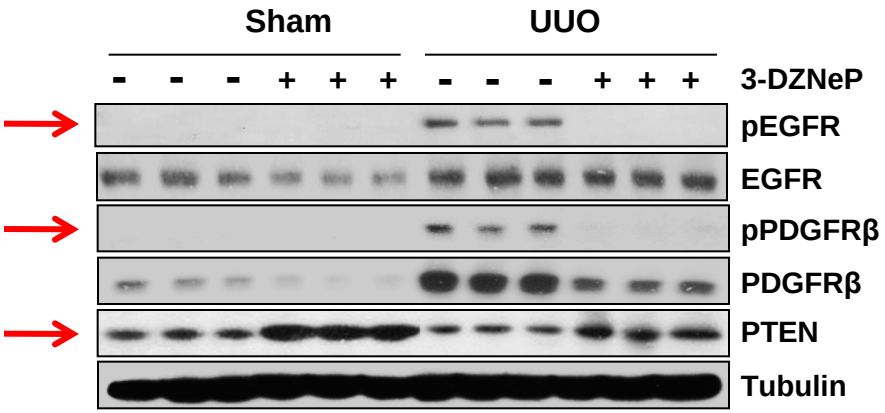
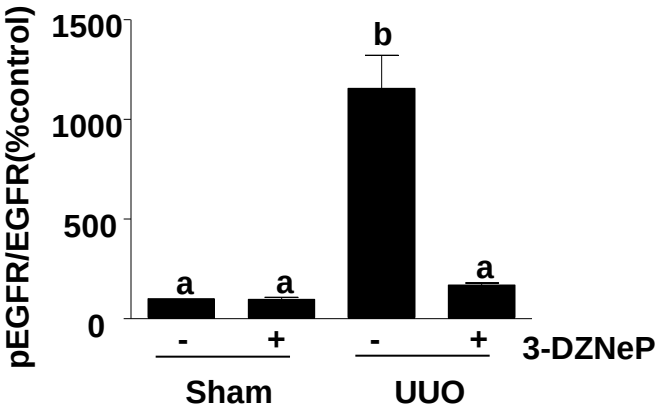
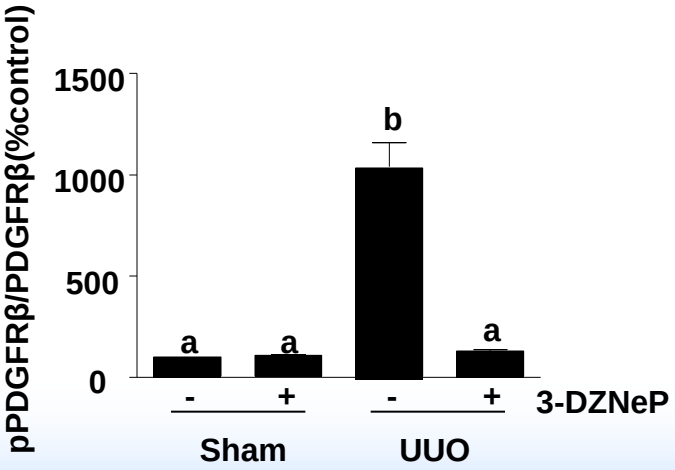
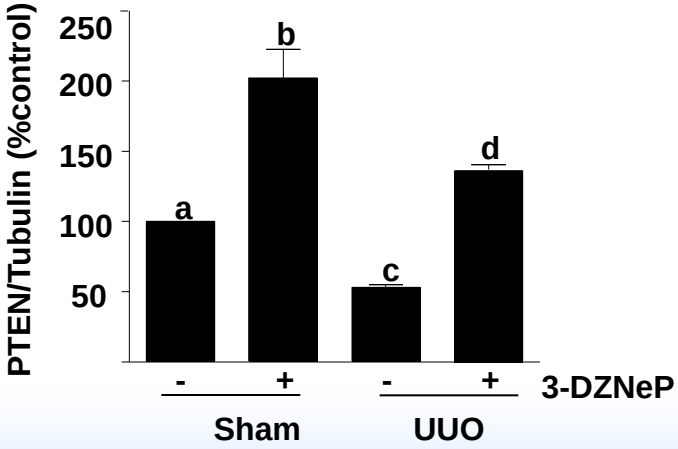
Blocking EZH2 inhibits phosphorylation of EGFR and PDGFRβ and up-regulation of PTEN in obstructed kidneys

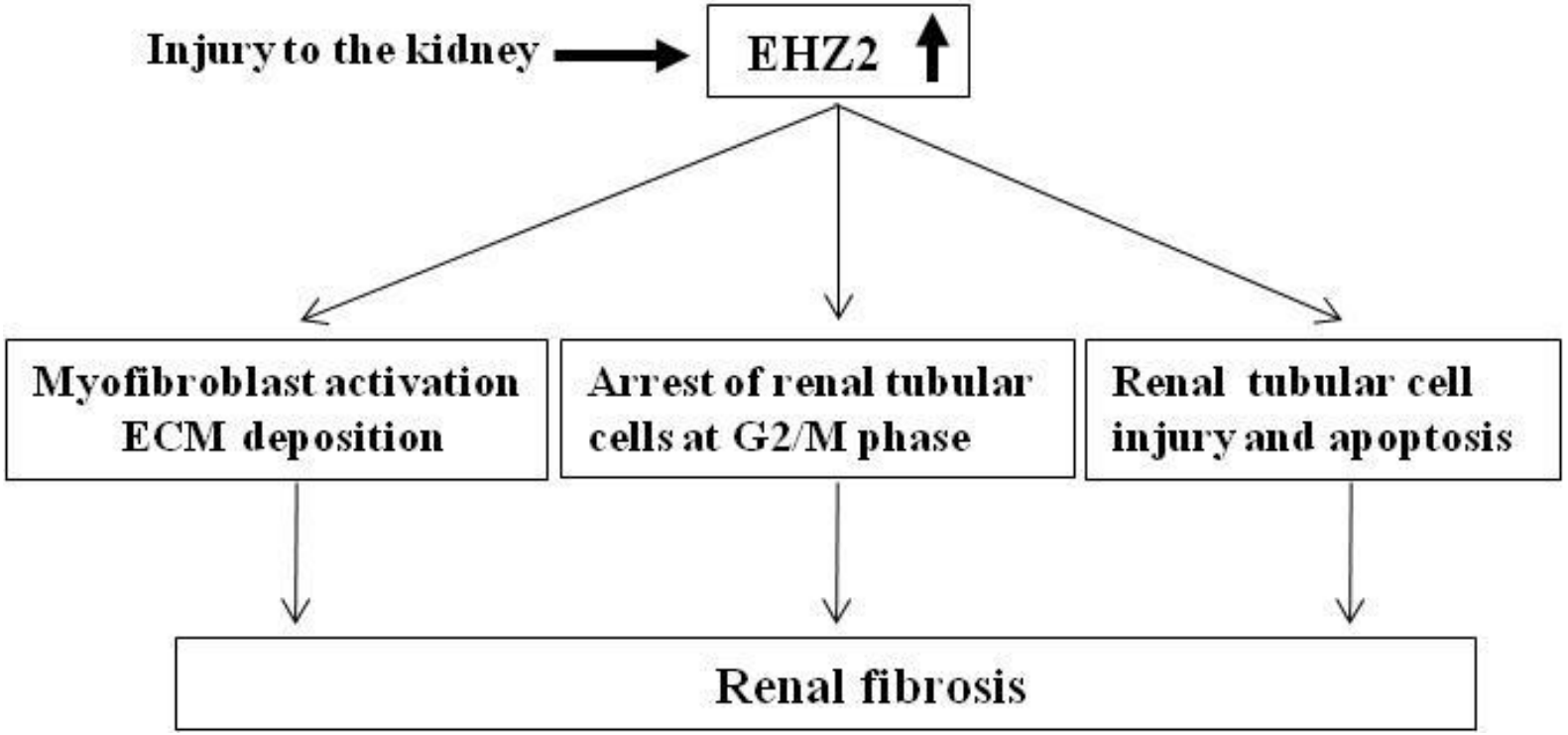


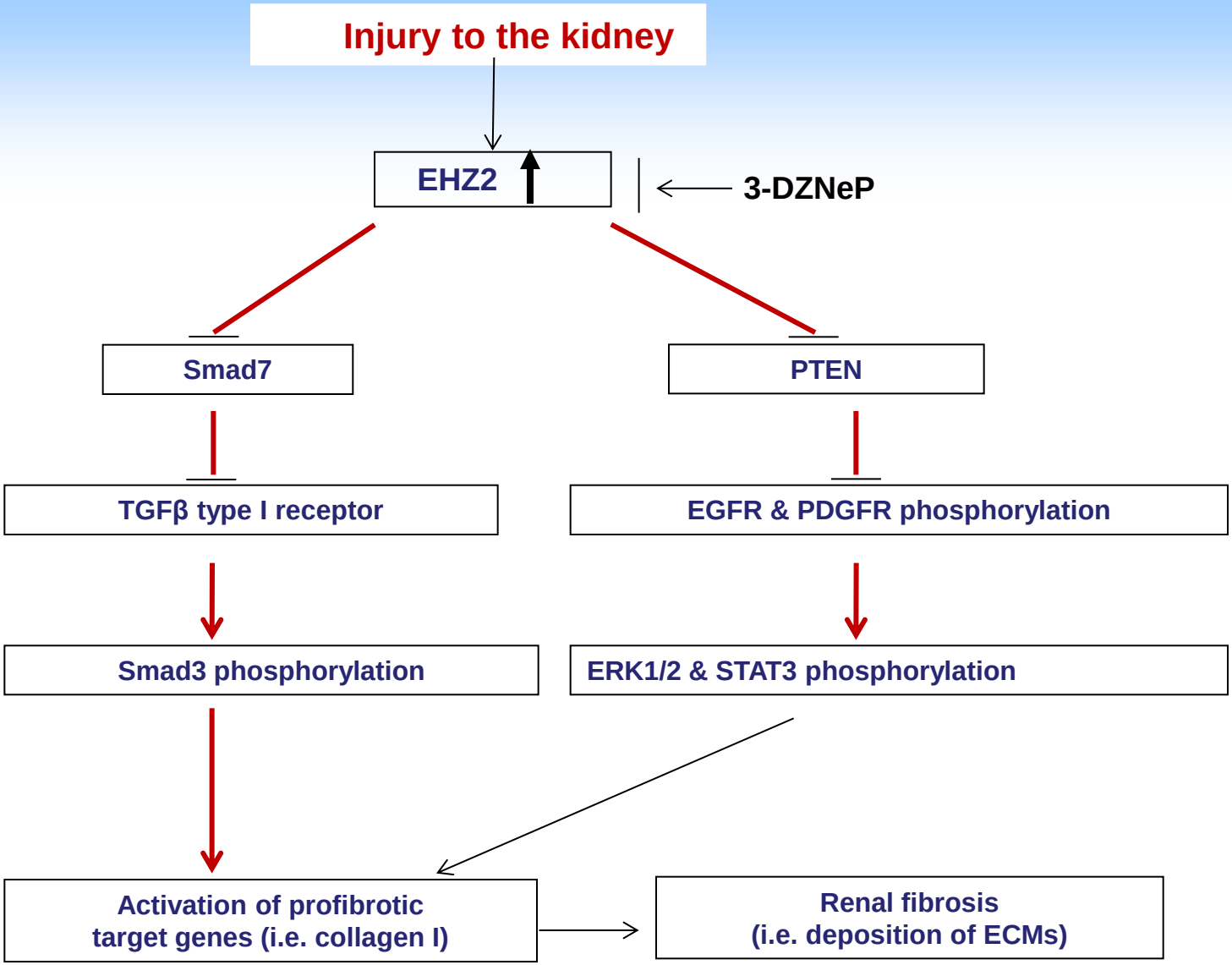






Mechanisms of EZH2-mediated renal fibrosis





EZH2 Inhibition Attenuates Renal Fibrosis by Maintaining Smad-7 and PTEN Expression

Clinical trials in CKD

	Surrogate outcomes*		Clinical outcomes	
	Measures	Trial results	Measures	Trial results
Kidney disease progression in CKD stages 1–4				
ACE inhibition and ARB *vs* other antihypertensive regimens	Decline in GFR and albuminuria	Slow decline in GFR (strong effect in patients with high baseline albuminuria); reduction in albuminuria	Time to kidney failure	Beneficial effect in patients with high baseline albuminuria
Low *vs* usual blood pressure target	Decline in GFR and albuminuria	Slow decline in GFR in patients with high baseline albuminuria; reduction in albuminuria	Time to kidney failure	Beneficial effect after long-term follow-up in patients with high baseline albuminuria; harm for target SBP<120 mm Hg in type 2 diabetes
More *vs* less intensive glycaemic control in diabetes	Decline in GFR and albuminuria	Inconsistent effects on GFR decline; reduction in albuminuria	Time to kidney failure	Not enough events; harm for target HbA_{1c}<6·0–6·5% in type 2 diabetes
Low protein diet with or without aminoacid or ketoacid supplements *vs* usual protein diets	Decline in GFR and albuminuria	Inconclusive effect on GFR decline; reduction in albuminuria	Time to kidney failure	Insufficient events
Statins *vs* placebo	Decline in GFR and albuminuria	Slow decline in GFR in some trials; reduction in albuminuria	Time to kidney failure	Insufficient events in small trials, generally non-significant outcomes in largest trial
Sodium bicarbonate *vs* standard care	Decline in GFR, nutritional status	Slow decline in GFR; improved nutritional status	Time to kidney failure	Beneficial effect in one small trial
Paricalcitol *vs* placebo	Decline in GFR and albuminuria	No effect on GFR decline; greater decline in albuminuria	Time to kidney failure	Not tested
Somatostatin *vs* placebo in PKD	Decline in GFR, cyst growth	No effect on GFR decline; small effect on cyst growth	Time to kidney failure	Not tested
mTOR inhibitors *vs* placebo or standard care in PKD	Decline in GFR and cyst growth	No effect on GFR decline; small effect on cyst growth	Time to kidney failure	Not tested