CTRR
Centre for Transplant and Renal Research

The Westmead Institute FOR MEDICAL RESEARCH

University of Sydney

NOVEL THERAPIES FOR CKD

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21/11/19

Westmead Hospital

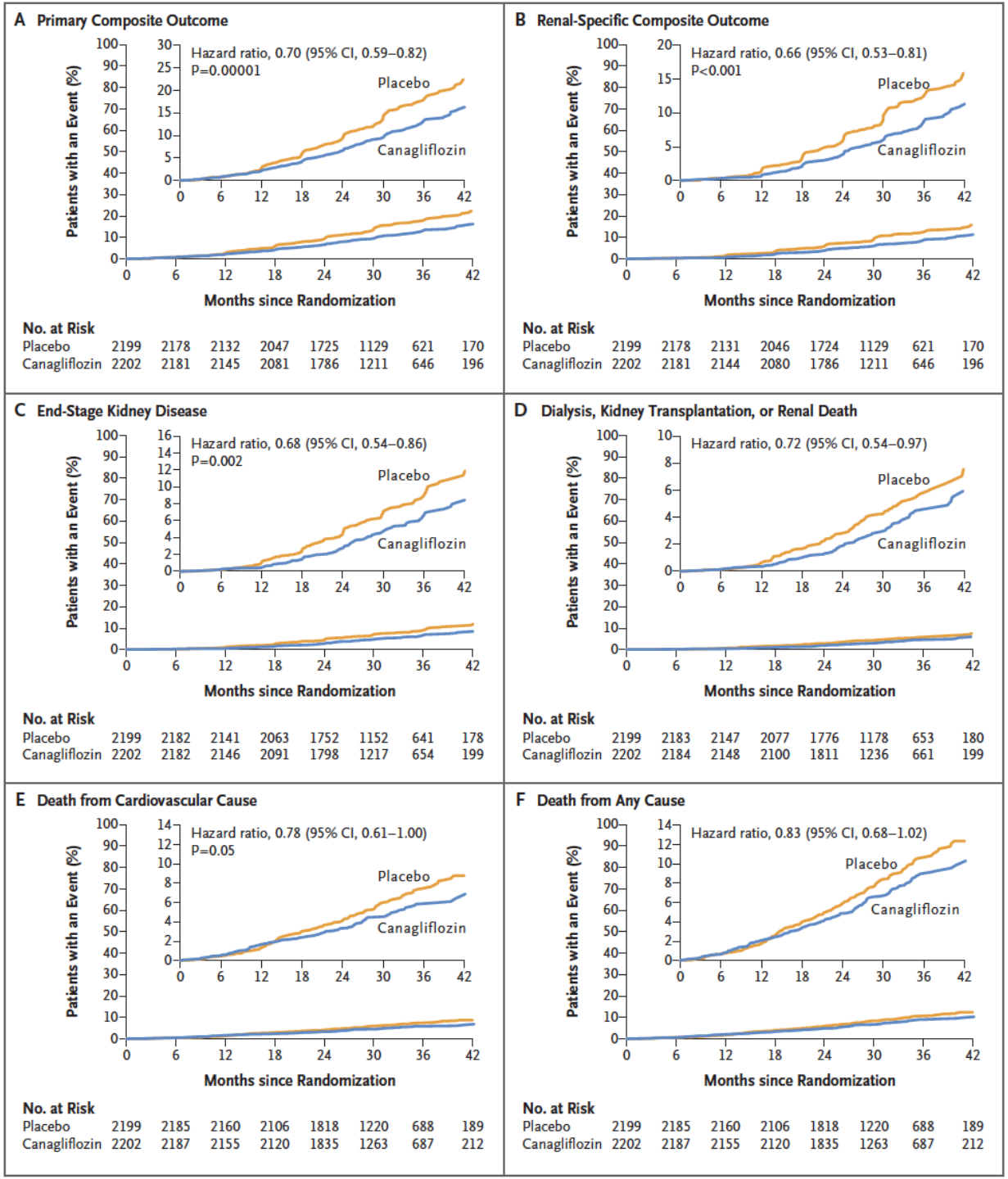
Post-ACEi doldrums….

Treat to help slow decline in kidney function and reduce hypertension risk*

- Lifestyle changes
  - Smoking cessation
  - Dietary salt restriction
  - Moderate alcohol consumption
  - Maintain BMI between 18.5 and 24.9 kg/m^2 through diet and exercise
  - Avoid more than two caffeinated drinks per day
- Blood pressure: assess and maintain blood pressure <130/80 mmHg with ACE inhibitor or ARB
- Cholesterol: maintain total cholesterol level <4.0 mmol/L with diet and statin
- Blood glucose (for patients with concurrent diabetes): aim for HbA_{1c} <7.0%
- Avoid nephrotoxic drugs and episodes of acute kidney injury

Cadnapaphornchai CJASN 2014;9:889

CREDENCE
NEJM 2019

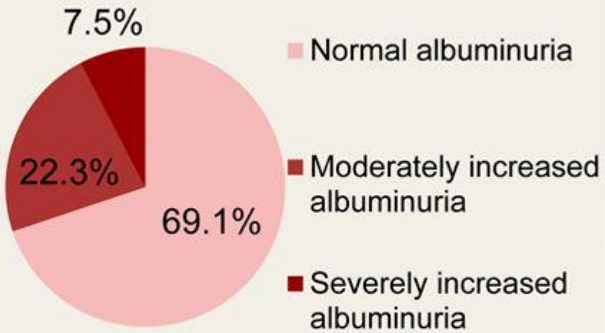


Effect of Canagliflozin on Renal and Cardiovascular Outcomes Across Different Levels of Albuminuria: Data From the CANVAS Program

METHODS

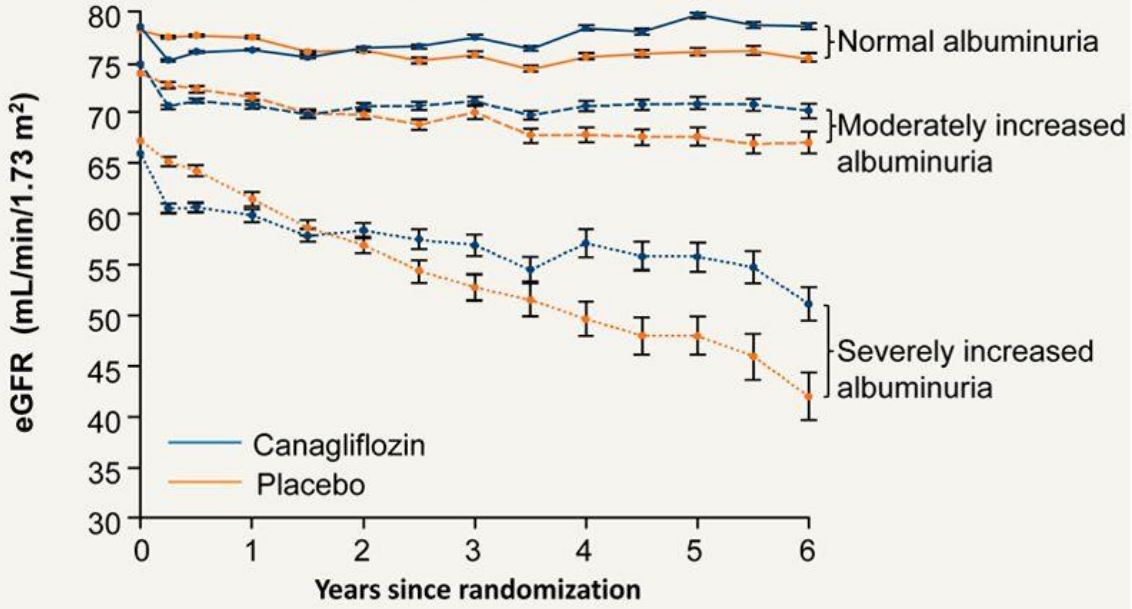
10,142 patients with T2DM

Canagliflozin Placebo



Note: 1.1% of patients did not have a UACR measurement at baseline.

RESULTS



CONCLUSION The proportional effects of canagliflozin on renal and cardiovascular outcomes are mostly consistent across different levels of albuminuria, but absolute benefits are greatest in people with severely increased albuminuria.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Brendon L. Neuen et al. JASN 2019;30:2229-2242

Ongoing renal and cardiovascular outcome trials in Type 2 Diabetes

Trial Name	Treatment	Number of participants	Primary Outcome	Planned completion date
VERTIS CV	Ertugliflozin	8000	Cardiovascular	2019
Dapa HF	Dapagliflozin	4744	Heart Failure	2019
FIDELIO-DKD	Finerinone	5734	**Renal**	2020
Dapa_CKD	Dapagliflozin	4000	**Renal**	2020
EMPOROR	Empagliflozin	8850	Heart Failure	2020
DELIVER	Dapagliflozin	4700	Heart Failure	2021
FIGARO	Finerinone	7437	Cardiovascular	2021
SCORED	Sotagliflozin	10,500	Cardiovascular	2022
EMPA-Kidney	Empagliflozin	5000	**Renal**	2022
SOUL	Semaglutide	9642	Cardiovascular	2024
FLOW	Semaglutide	3160	**Renal**	2024

Perkovic V. ASN Kidney News 2019

PROGRESSION OF POLYCYSTIC DISEASE
Current/recent trials

mTOR inhibitors (sirolimus, everolimus)

somatostatin analogues (octreotide)

V2 antagonists (tolvaptan)

(statins)

(ACEi & ARBs)

TRANSLATION OF SMALL MOLECULAR ANTI-FIBROTICS

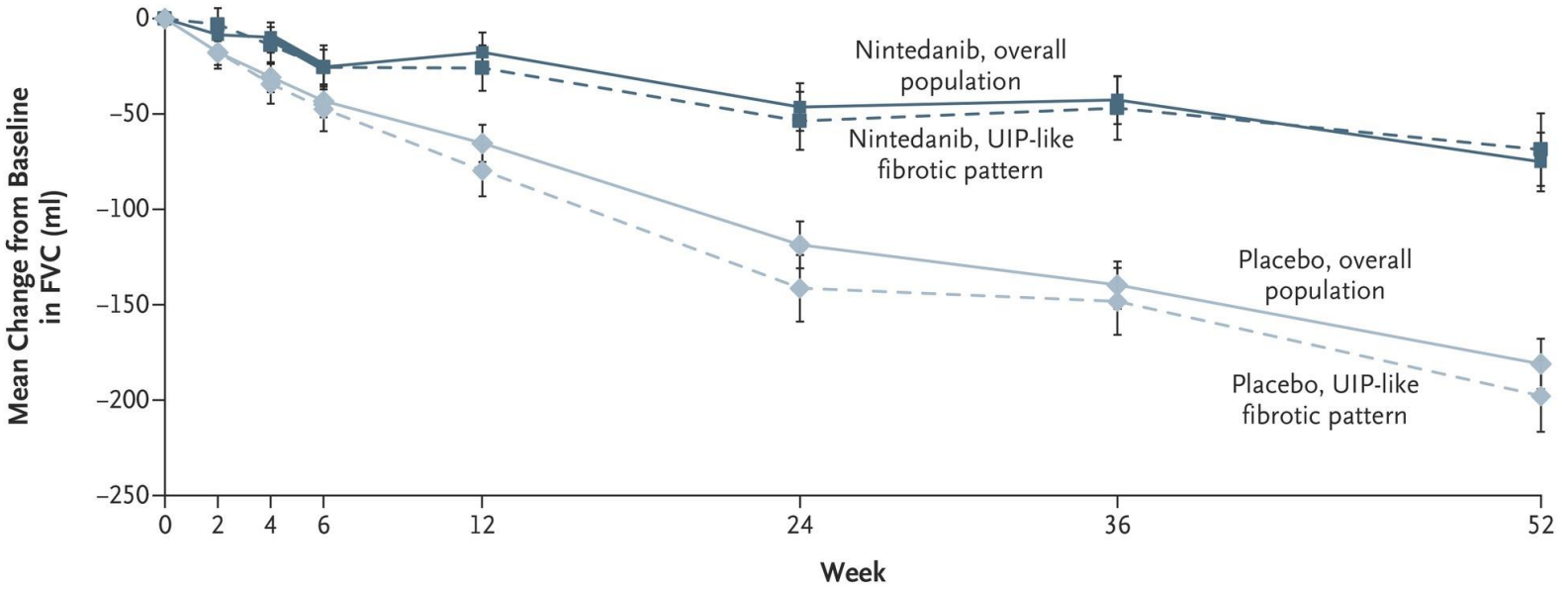
N=63, mainly for respiratory (IPF), liver (NASH, NAFLD), and skin (scleroderma, keloid) diseases

N=11 for renal disease

Pirfenidone	**multiple**	**diabetic nephropathy (DN, phase 2, completed)**
F-351	**p38 (α,γ) inh**	**(liver &) kidney fibrosis (phase 1b/11)**
Atrasentan	**sel ETAr inh**	**DN (phase 111, SONAR)**
GKT-137831	**NOX1 & NOX4 inh**	**DN (phase 11)**
Bardoxolone	**NRF2-KEALi act**	**CKD & DN (phase 111, terminated—safety)**
Baricitinib	**JAK1 & JAK2 inh**	**DN (phase 11)**
Emricasan	**pan-caspase inh**	**severe renal impairment (phase 1)**
Beraprost	**prostacyclin analogue**	**primary glom disease (phase 11b/111)**
CTP-499	**pan-PDE inh**	**DN (phase 11, completed)**
Pyridoxamine	**metabolite of vit B6**	**DN (phase 11, completed)**
Bindarit	**CCL3, -7, -8 inh**	**DN (phase 11, completed)**

Nanthakumar CB et al. Nat Rev Drug Discovery 2015;14:693-720

Nintedanib for interstitial lung disease



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

IC inhibitor of tyrosine kinases

Flaherty KR. NEJM 2019;381:1718-1727

Novel anti-fibrotic drugs in clinical trials

INHIBITORS

- NFκB
- TNFα
- JAK-STAT
- chemokines
- leucocyte migration
- PPAR
- NOX
- endothelin receptor
- TGF-β
- CTGF
- uric acid
- SGLT-2
- DPP-4
- GLP-1R
- galectin-3
- PDE

ACTIVATORS

- Nrf2
- BMP-7
- vitamin D receptor

Table 1. Novel anti-fibrotic drugs in clinical trials

Phase	Group	Drug	RAAS blockade association	Kidney disease	Outcome	Status	Reference
Priming phase	NFkB blockers	ACTHar gel		DKD	Slowed the rate down of GFR decrease, reduced proteinuria		28
		ACTHar gel		DKD		Ongoing	NCT01028287
		Bindarit		DKD	Reduced albuminuria		29
							NCT01109212
	TNF-α blockers	Adalimumab		Primary FSGS	No effects on proteinuria reduction		33, 34
	JAK-STAT inhibitors	Baricitinib		DKD	Reduced albuminuria, no changes in kidney function		39
	Chemokine antagonists	Emapticap pegol		DKD	Reduced albuminuria		43
		PF-04634817			No effects on proteinuria reduction or on kidney function		NCT01712061
		CCX140-B	Yes	DKD	Reduced albuminuria		46
	Leukocyte migration inhibitors	Colchicine		Renal transplant	Prevent the development of interstitial fibrosis		54
		ASP8232	Yes	DKD, CKD		Ongoing	NCT02358096
	PPAR antagonists	Fenofibrate		DKD	Reduced albuminuria, slowed the rate down of GFR decrease		68, 69
		Rosiglitazone		DKD, non diabetic nephropathies	Reduced albuminuria and proteinuria		70, 71
	NOX inhibitors	GKT137831		DKD	No effects on albuminuria reduction		75, NCT02010242
		Setanserin		DKD		Ongoing	76
	Nrf2 activator	Bardoxolone		DKD, CKD Alport	Slowed the rate down of GFR decrease, increased albuminuria		85, 93
		Bardoxolone		DKD	Slowed the rate down of GFR decrease		86, 92
		Bardoxolone		DKD, CKD		Ongoing	NCT02316821
		Bardoxolone		Alport		Ongoing	NCT03019185
Activation phase	Endothelin receptor antagonists	Atrasentan	Yes	DKD	Reduced albuminuria		98, 99
		Atrasentan	Yes	DKD		Ongoing	NCT01424319
		Avosentan	Yes	DKD	Reduced albuminuria		96
		Sparsentan	Yes	FSGS	Reduced proteinuria		101
		TAK-044		CKD	No effects on GFR decline		95
Execution phase	TGF-β blockers	Fresolimumab		FSGS	Slowed the rate down of GFR decrease		109
		Fresolimumab		FSGS	No effect on proteinuria reduction		110
		Pirfenidone		FSGS	Slowed the rate down of GFR decrease, no effects on proteinuria		113
		Pirfenidone		DKD	No changes in kidney function		114
		Pirfenidone		CKD		Ongoing	NCT02406794
		Pirfenidone		DKD		Ongoing	NCT02698774
	CTGF blockers	FG-3019		DKD	Reduced microalbuminuria		115
	BMP-7 agonists	THR-184		CKD	No effects on GFR decline, reduced incidence of AKI		NCT01830920
Progression phase	Uric acid lowering drugs	Allopurinol		CKD, DKD	No effect on proteinuria, blood pressure or serum creatinine		121, 122, 123, 124
		Febuxostat		CKD	Reduced albuminuria, no changes in kidney function		125
		Febuxostat		DKD	No effects on proteinuria or GFR decline		126
	SGLT-2 inhibitors	Empagliflozin		CKD, DKD	Reduced albuminuria and slowed the rate down of GFR decrease		128
		Canagliflozin	Yes	CKD, DKD		Ongoing	NCT02065791
	DPP-4 inhibitors	Saxagliptin		CKD, DKD	Reduced albuminuria		135
		Saxagliptin		CKD, DKD		Ongoing	NCT02462369
		Sitagliptin	Yes	CKD, DKD	Reduced albuminuria		136
		Linagliptin	Yes	CKD, DKD	No effects on albuminuria		144
		Linagliptin		CKD, DKD		Ongoing	NCT02376075, NCT01897532
	GLP-1R inhibitors	Exenatide		CKD, DKD	Reduced albuminuria		137
		Exenatide	Yes	CKD, DKD	No effects on proteinuria or on GFR decline		146
		Exenatide	Yes	CKD, DKD		Ongoing	NCT03029351
		Liraglutide	Yes	CKD, DKD	Reduced albuminuria		138, 140, 141, 142, 143
		Liraglutide		CKD, DKD	Reduced albuminuria		139
		Liraglutide	Yes	CKD, DKD	No effects on GFR decline		145
		Liraglutide	Yes	CKD, DKD		Ongoing	NCT02545738
	Vitamin D receptor activators	Paricalcitol	Yes	DKD	Reduced albuminuria		148
		vitamin D3	Yes	CKD, DKD	Reduced proteinuria		152, 153
	Galectin-3 antagonists	GCS-100		CKD	Slowed the rate down of GFR decrease		NCT01843790
	PDE inhibitors	Pentoxifylline	Yes	CKD, DKD	Reduced albuminuria		163, 166
		Pentoxifylline	Yes	CKD, DKD		Ongoing	NCT01377285, NCT03006952
		Pentoxifylline	Yes	CKD, DKD	No effect on albuminuria, slowed the rate down of GFR decrease		168
		Pentoxifylline		CKD, DKD	Reduced albuminuria		164
		Pentoxifylline		CKD, DKD	Slowed the rate down of GFR decrease		NCT01382303
		Pentoxifylline		AKI		Ongoing	NCT02951299
		Pentoxifylline	Yes	CKD, DKD	Reduced proteinuria, slowed the rate down of GFR decrease		165, 167
		Pentoxifylline	Yes	CKD, DKD	No effects on proteinuria or GFR decline		169, 170
		Pentoxifylline	Yes	CKD	No effect on albuminuria, slowed the rate down of GFR decrease		162
		Pentoxifylline	Yes	CKD	Reduced albuminuria		161
		CTP-499		DKD	Slowed the rate down of GFR decrease, no effect on albuminuria		171
		PF-00489791		DKD	Reduced albuminuria		172

Allinovi M et al. Matrix Biol 2018

Novel anti-fibrotic drugs tested in clinical trials, prematurely interrupted

Phase	Group	Drug	Target	RAAS blockade association	Kidney disease	Status and adverse effects	Effects	Reference
Priming phase	NFkB blockers	Bindarit	MCP-1		DKD, CKD	Discontinuation of clinical development of the drug		29
	Chemokine antagonists	MLN1202	CCR2		DKD, CKD	Prematurely stopped for unknown reasons		NCT02410499
		BMS-813160	CCR2/CCR5		DKD	Discontinuation of clinical development of the drug		NCT01752985
		Bardoxolone	Nrf2	Yes	DKD, CKD	Prematurely terminated for high rate of cardiovascular events	Did not reduce the risk of ESRD or death	89
		Gevokizumab	IL-1β		DKD	Prematurely terminated		[211]
Activation and execution phase	Endothelin receptor antagonists	Atrasentan	ET-1	Yes	DKD, CKD		Prematurely stopped due to lack of efficacy	NCT01858532
		Avosentan	ET-1	Yes	DKD	Trial stopped because of fluid retention	Reduced albuminuria	97
	Integrin blockers	STX-100	α5β6 integrin		Renal transplant	Prematurely stopped for unknown reasons		NCT00878761
	TGF-β blockers	LY2382770	TGF-β		DKD, CKD		Prematurely stopped due to lack of efficacy	111
	CTGF blockers	FG-3019	CTGF		FSGS	Prematurely stopped for unknown reasons		NCT00782561
		FG-3019	CTGF	yes	DKD, CKD	Prematurely stopped for suboptimal study design		NCT00913393
Progression phase	Galectin-3 antagonist	GCS-100	galectin-3		DKD	Discontinuation of clinical development of the drug because the Company was required to conduct additional chemical characterization	Mild increase of GFR	154

ACTIVATORS

Nrf2

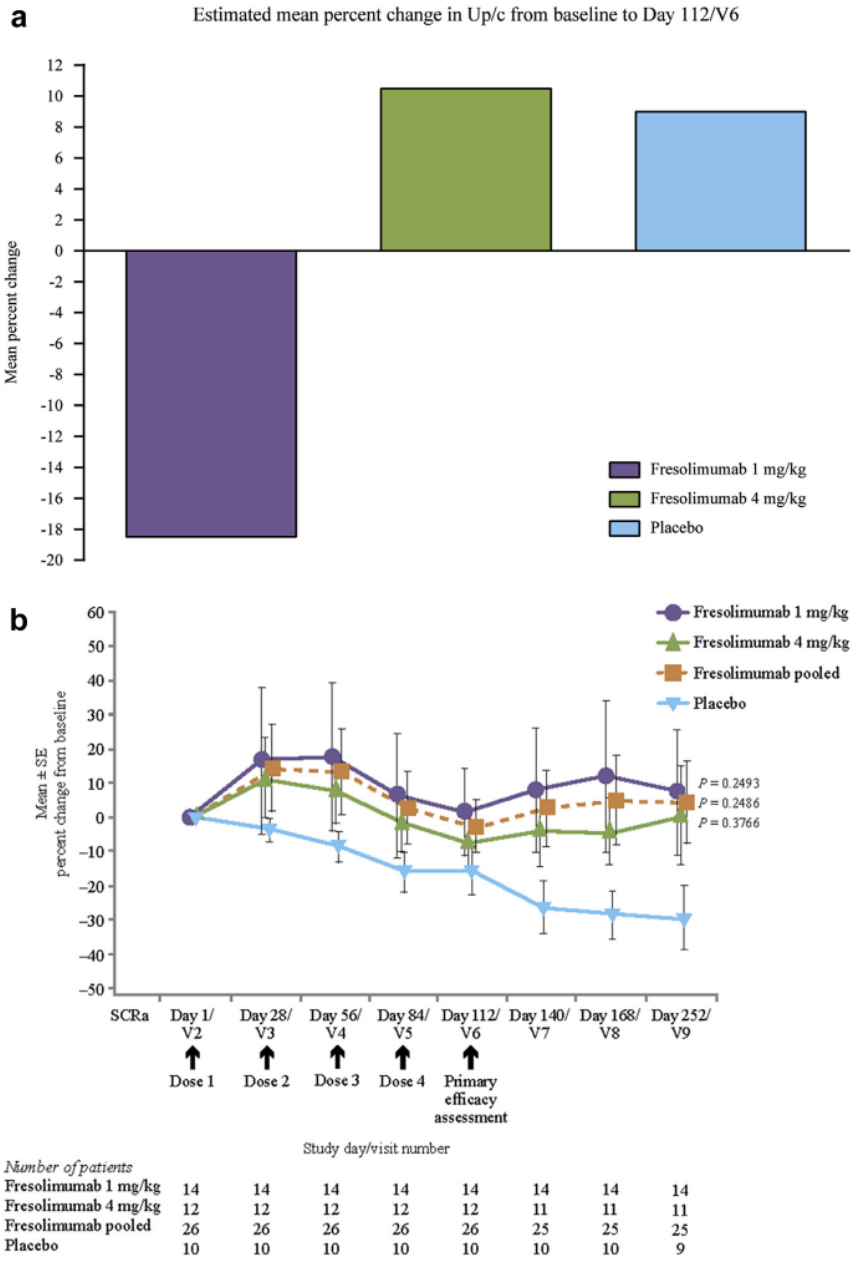
INHIBITORS

NFκB
chemokines
IL-1β
endothelin receptor
integrin
TGF-β
CTGF
galectin-3

Allinovi M et al. Matrix Biol 2018

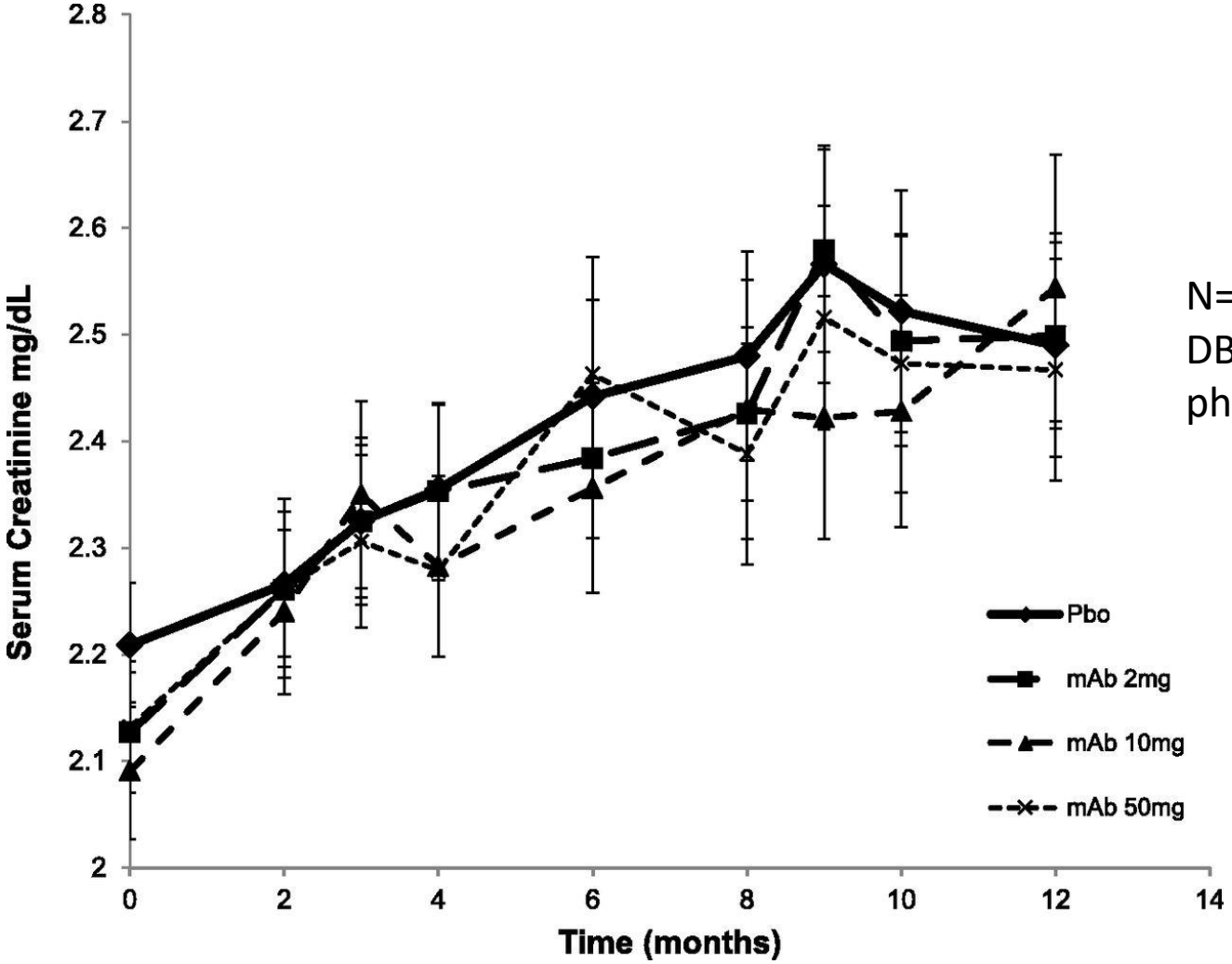
SR-FSGS fresolimumab trial terminated

N=36
DB, randomised



Vincenti F et FGS Study Group
KIR 2017:2:800-810

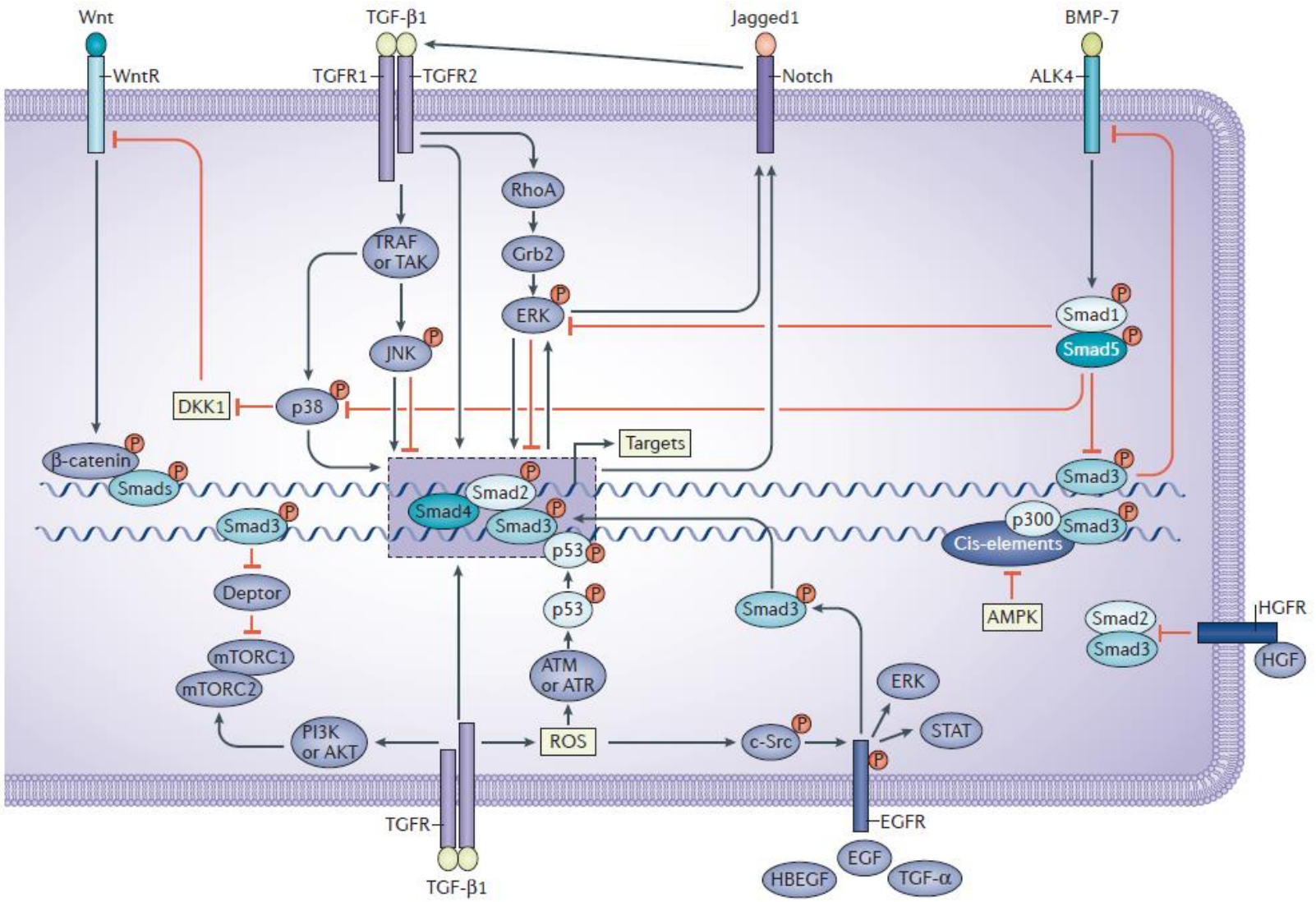
TGF-β1 mAb for DN trial terminated



N=416
DB, randomised
phase 2

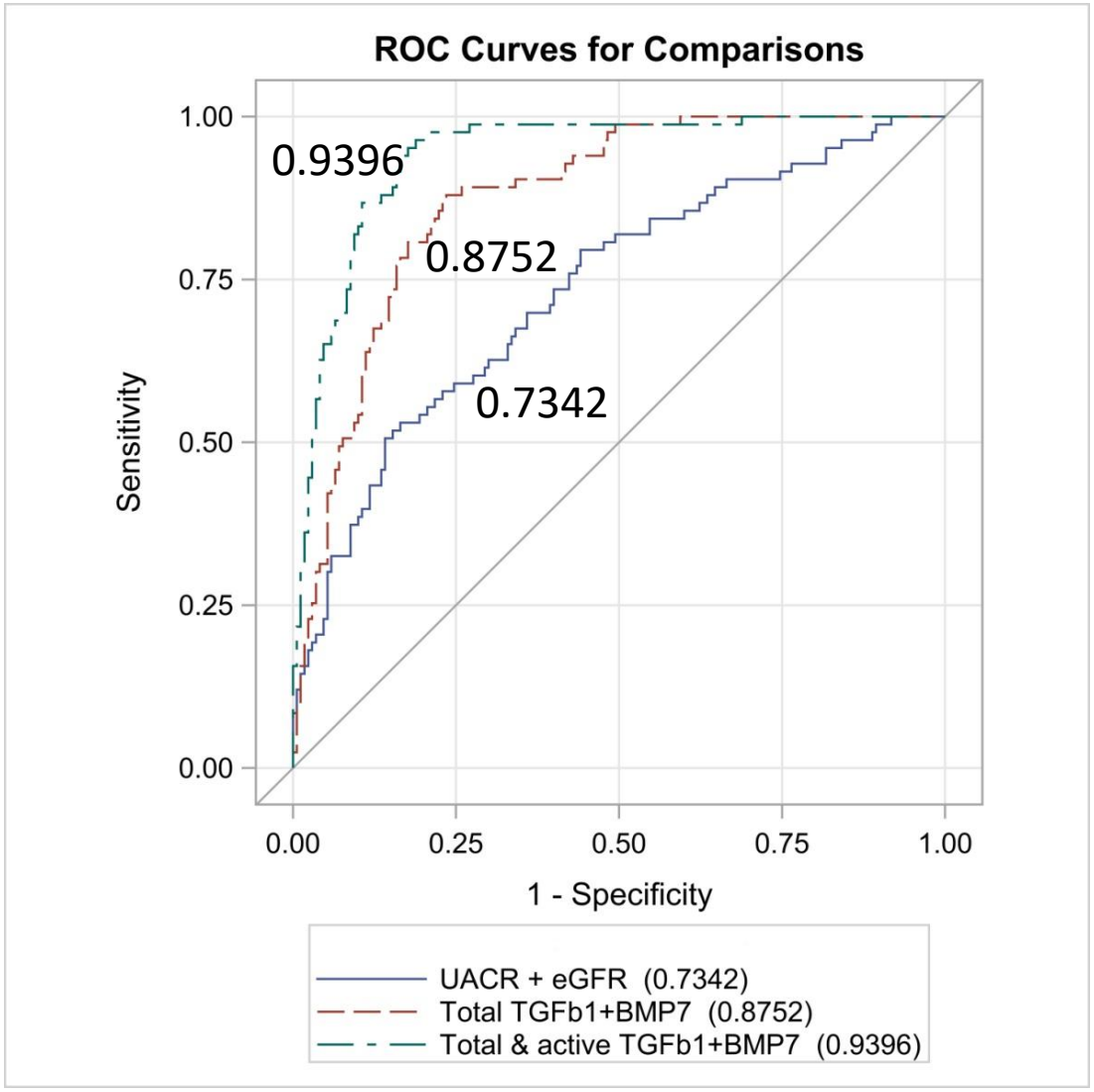
Voelker J et al. JASN 2017;28:953-962

TGF-β: the master regulator of fibrosis



Meng X-M et al. NRN 2016;12:325-38

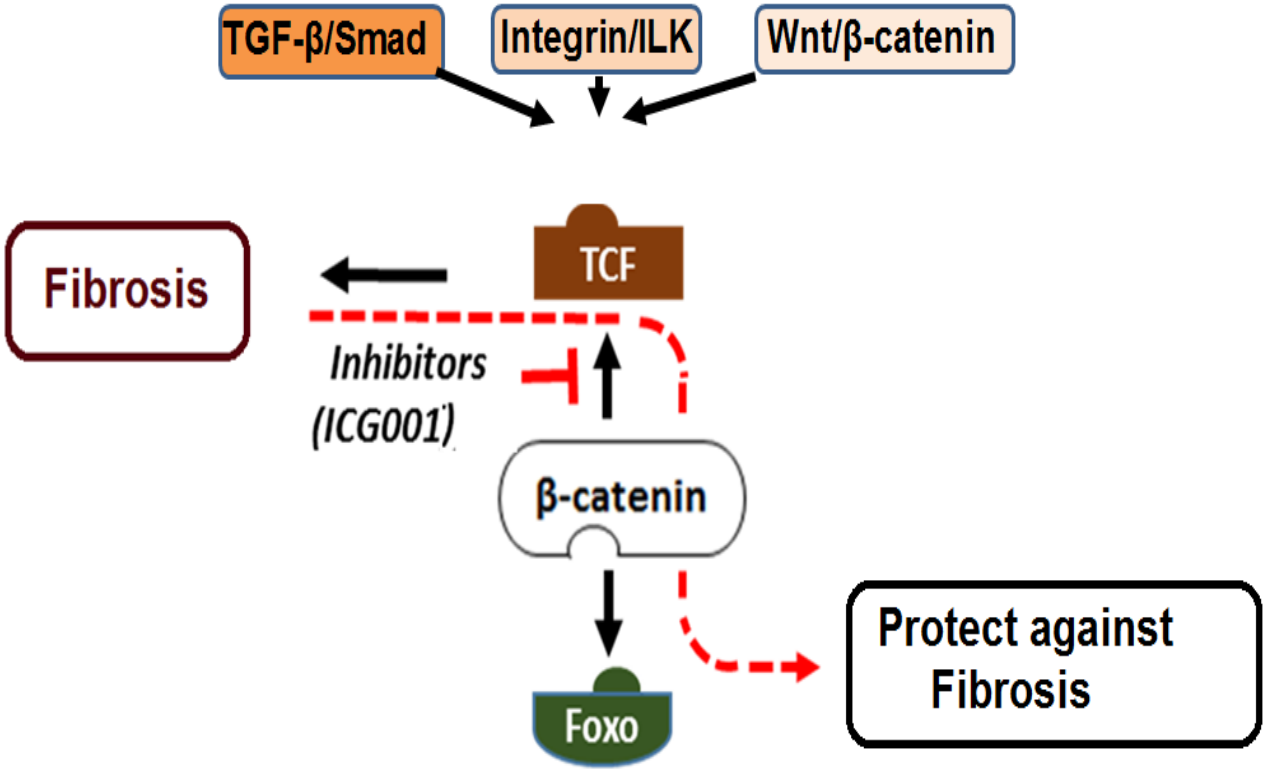
BMP7 and TGFβ1 are better predictors of major renal endpoints than eGFR+UACR



baseline serum
TREAT participants (n=1000)

Wong et al. KI 2013

TGF-β causes tissue fibrosis through three major Signaling Pathways

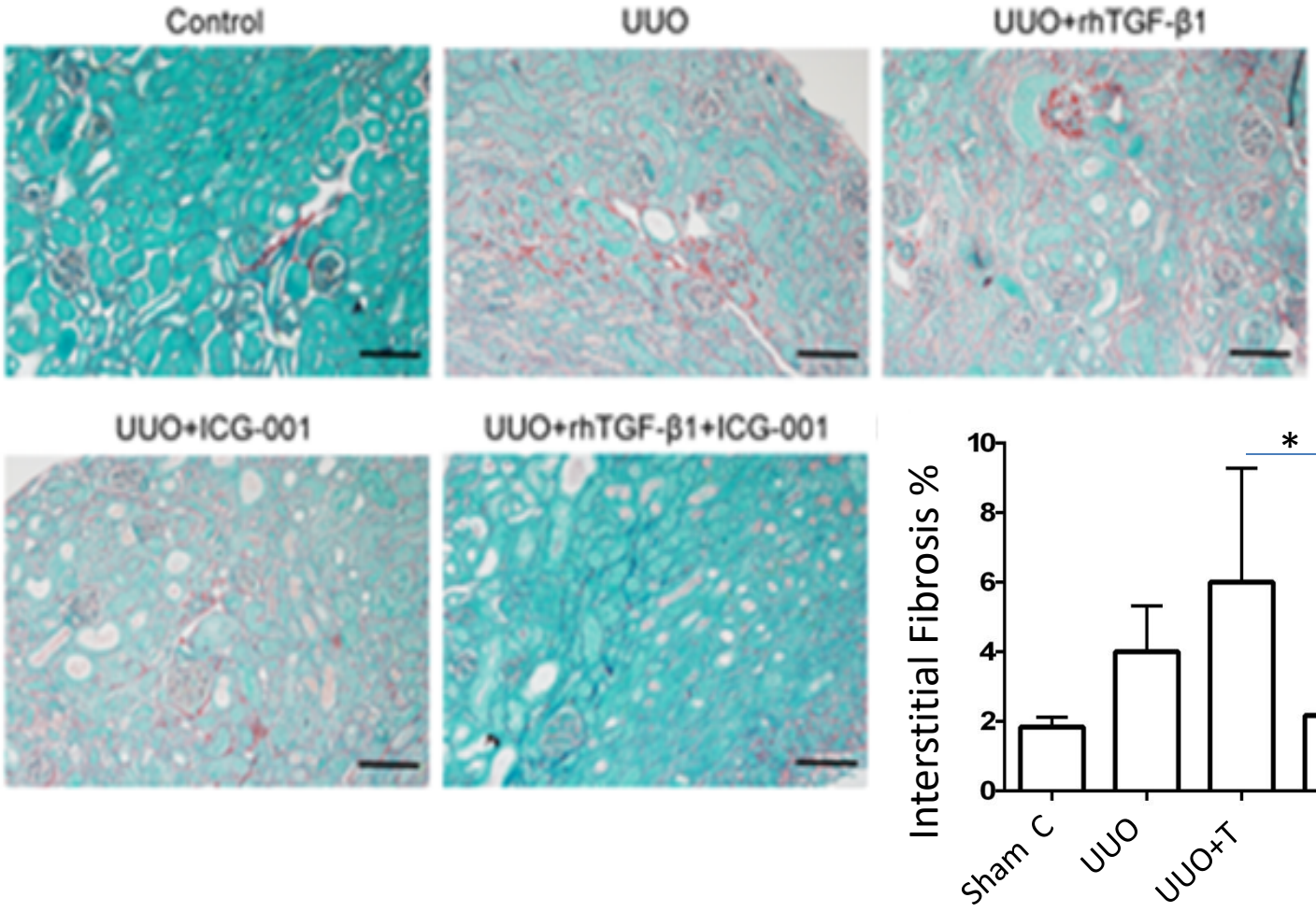


Hypothesis: β-catenin/Foxo is the key target to dissociate profibrotic from anti-inflammatory and wound-healing effects of TGF-β

Anti-fibrotic effect of β-catenin/Foxo

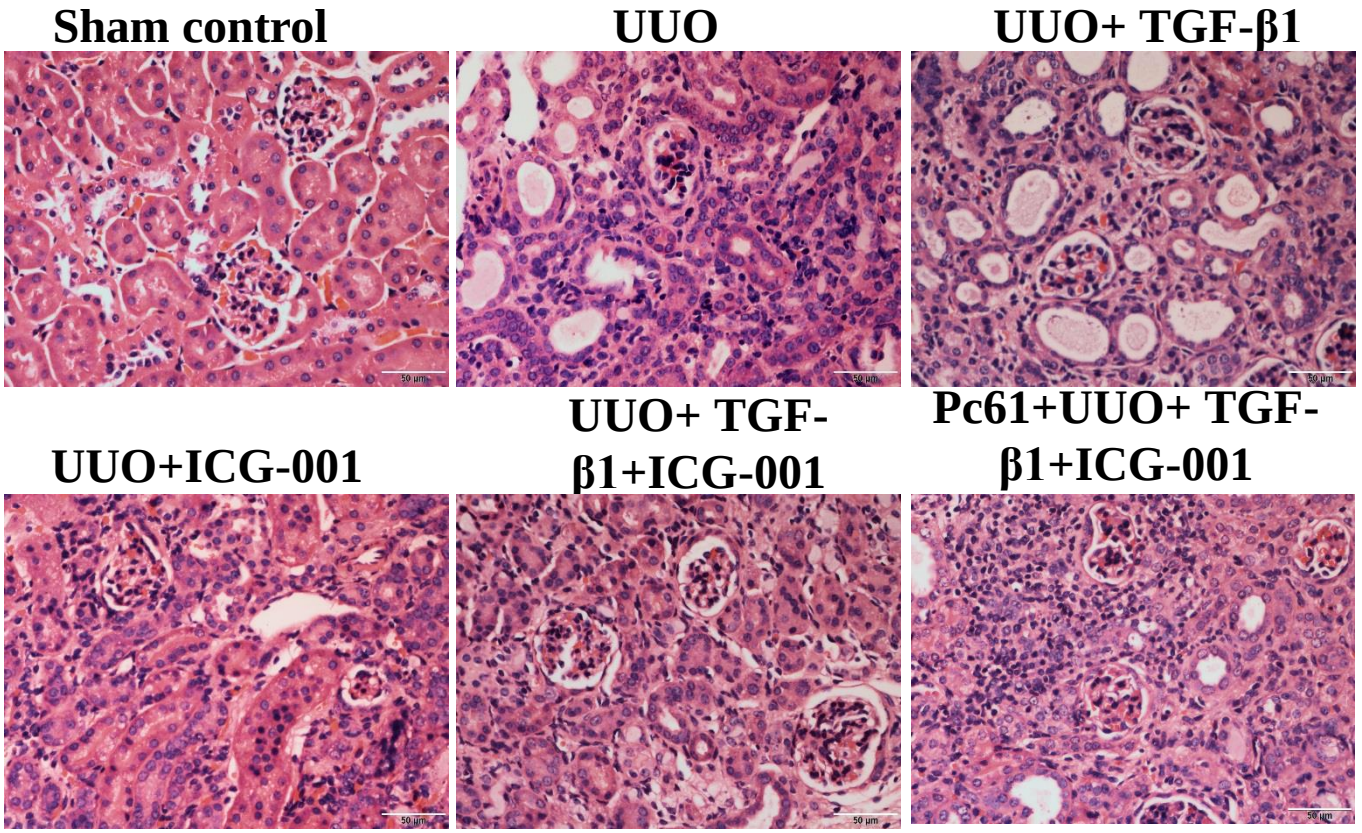
Rao P, Zheng G, Harris DC

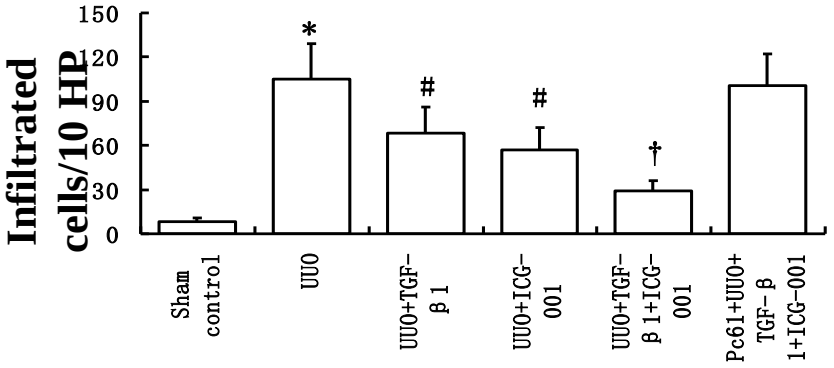
Inhibition of β-catenin/TCF interaction by ICG-001 decreases kidney fibrosis



Treg-dependent anti-inflammatory effect of β-catenin/Foxo

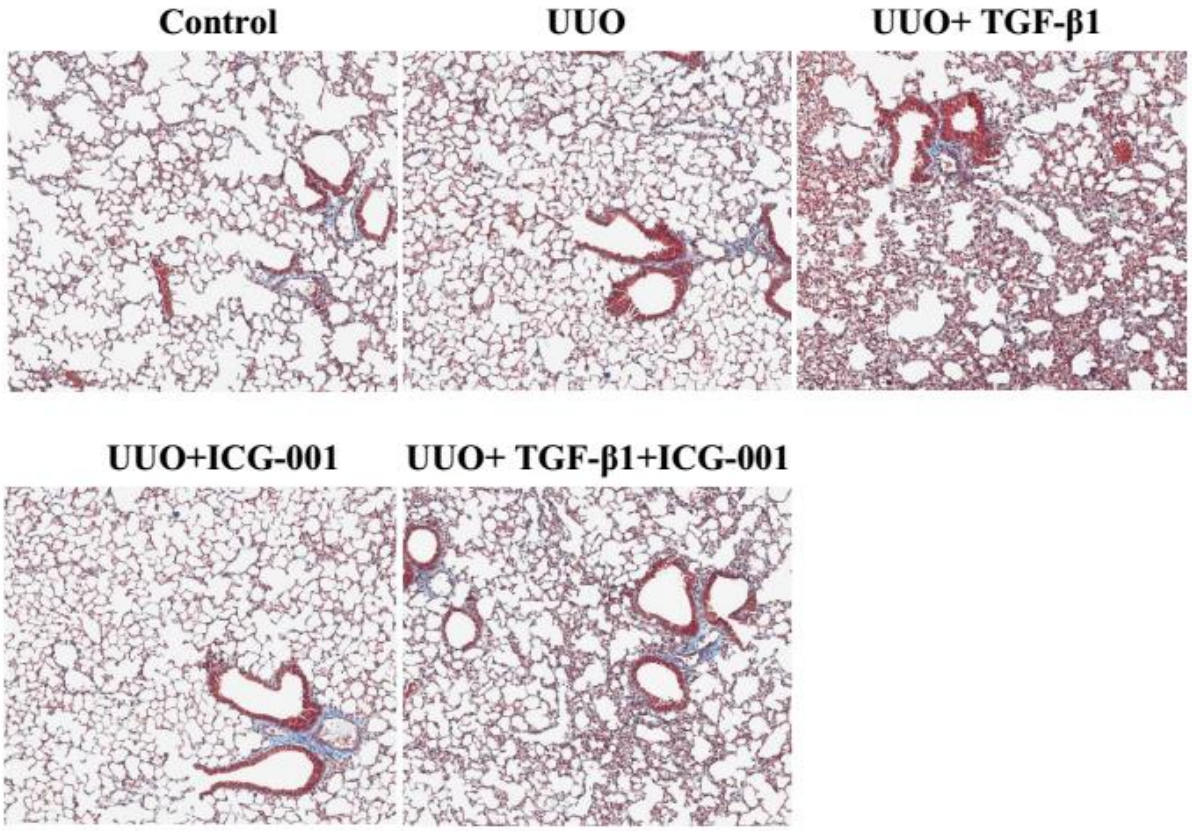
Inhibition of β-catenin/TCF interaction by ICG-001 reduces inflammation via iTreg in UUO kidney

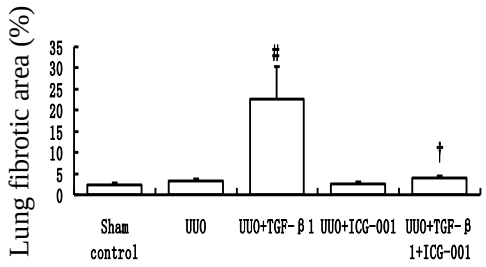




*$P < 0.05$ vs control
# $p < 0.05$ vs untreated UUO
†$p < 0.05$ vs TGF-β1 treated UUO

Inhibition of β-catenin/TCF interaction by ICG-001 prevents TGF-β1-induced distant organ fibrosis (lung)



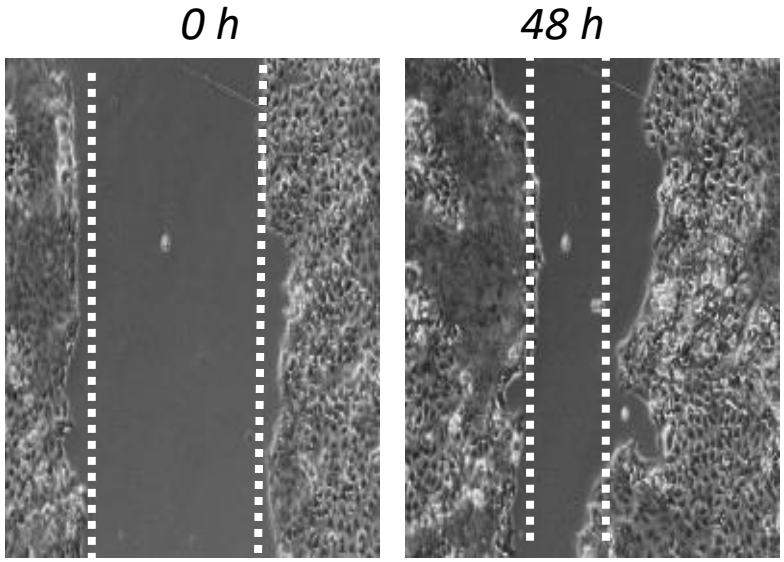


 # $p < 0.05$ vs untreated UUO
† $p < 0.05$ vs TGF-β1-treated UUO

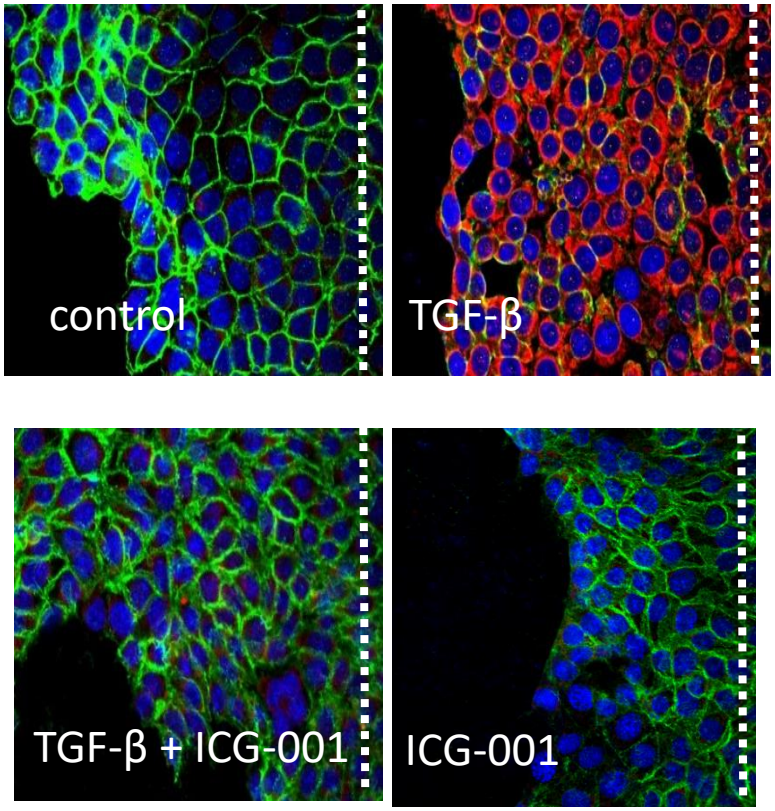
non-fibrotic wound-healing effect of β-catenin/Foxo in kidney injury

β-catenin/Foxo1 promotes non-fibrotic wound healing *in vitro*

***In vitro* Scratch Assay**



IF staining of E-cadherin / α-SMA



Therapeutic targeting β-catenin/Foxo by inhibition of β-catenin/TCF…….

reduces

fibrosis (kidney, lung, liver)

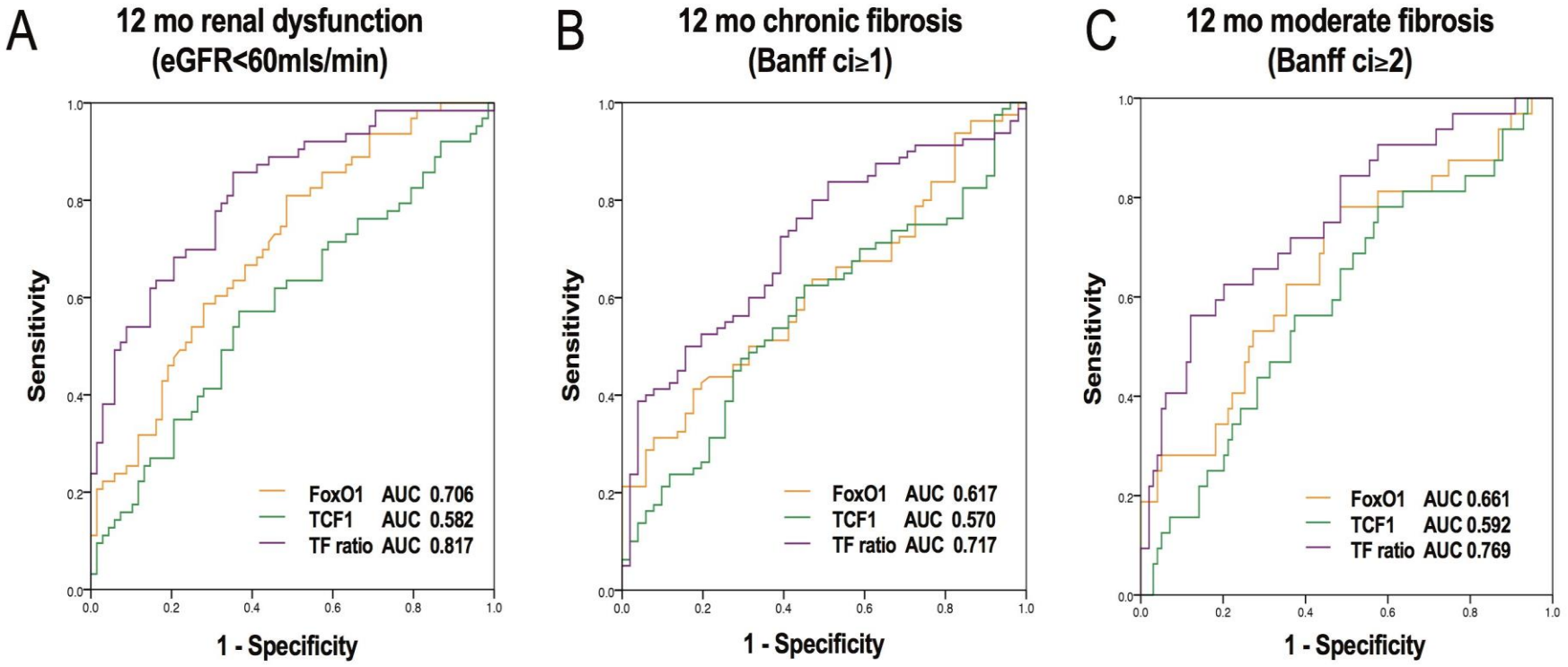
infiltration of lymphocytes & macrophages, (Treg-dependent)

increases

non-fibrotic wound healing

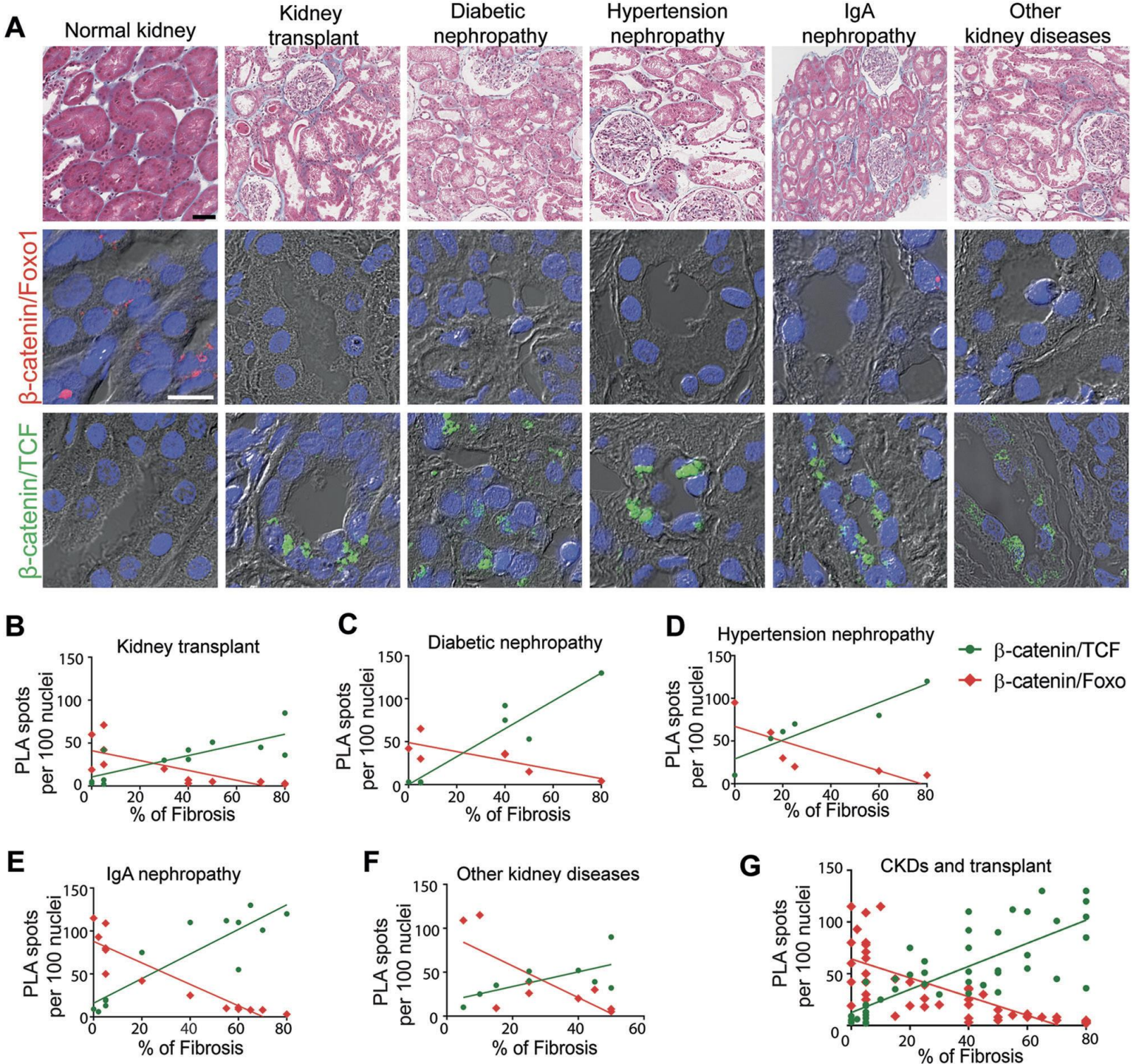
Binding of β-catenin to TCF1 or FoxO1 controls fibrogenic signalling pathways & predicts adverse outcomes in transplanted kidneys

1-month biomarkers predicting adverse clinical outcomes



Yang Y, Nankivell B, Zheng G, Harris DC

Rao P
Lab Inv 2019



TARGETING INFLAMMATION

DNA VACCINATION

chemokines/receptors: CCL2, CCL5, CX3CR1
costimulatory molecules: CD40

INHIBITING EFFECTOR CELLS

REGULATORY CELLS

(mesenchymal stem cells)
protective macrophages: M2a, M2c, Mreg
tolerogenic dendritic cells
regulatory lymphocytes
regulatory innate lymphoid cells