18th Asian Colloquium in Nephrology

SOTANC

Best Practices in Kidney Care in Asia 19 – 21 July 2019

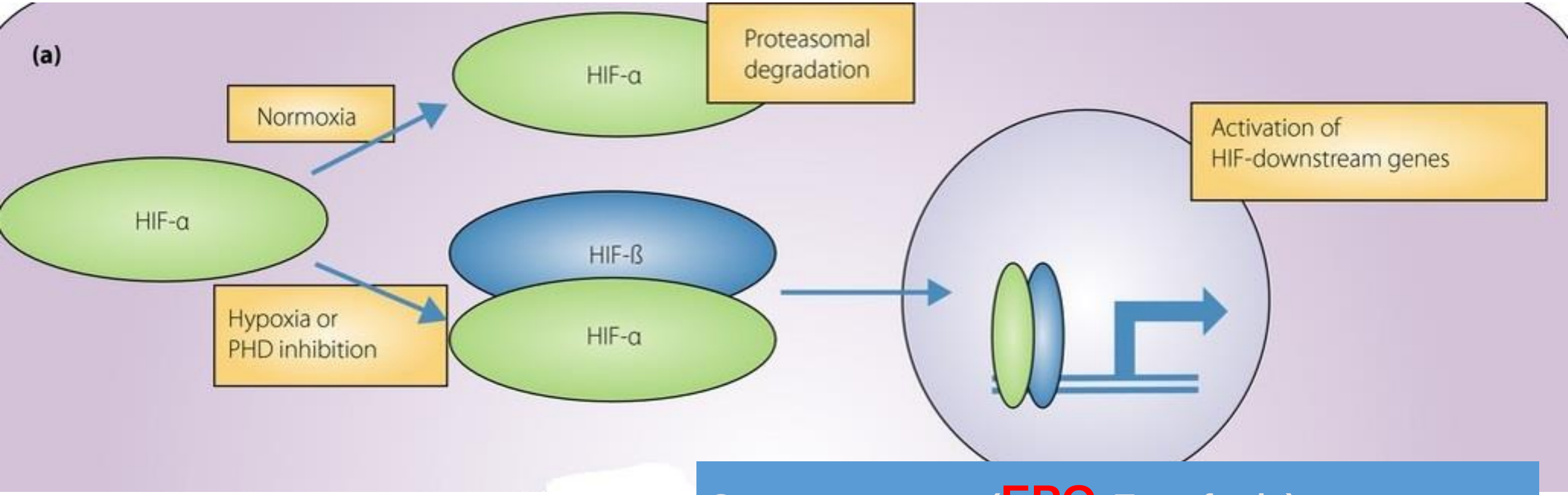
Incorporating: SOTANC - State-Of-The-Art Nephrology Course (Nursing)
Singapore Society of Nephrology Annual Scientific Meeting
Asia Renal Association - Asian Nephrology Conference

Anemia in CKD/ESKD: Is it still EPO?"

Masaomi Nangaku

Division of Nephrology and Endocrinology
the University of Tokyo Graduate School of Medicine

Cellular responses against anemia and hypoxia



Oxygen transport (**EPO**, Transferrin)

Vascular regulation (VEGF, adrenomedullin, HO-1)

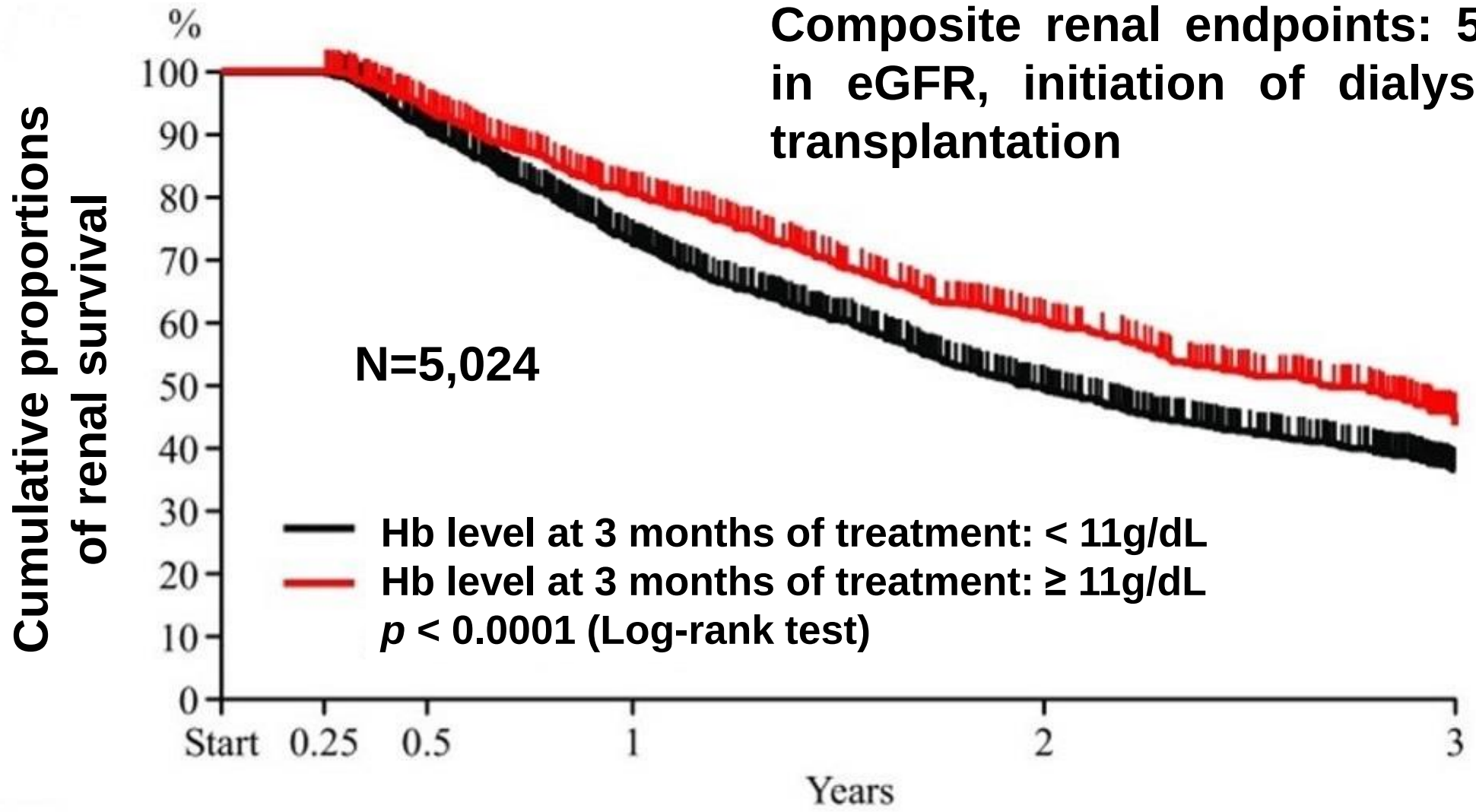
Glucose uptake and glycolysis (Glut-1, Aldolase A)

Anti-oxidative enzymes (SODs, catalase)

Hirakawa, Nangaku, et al. J Diabetes Investig 2017

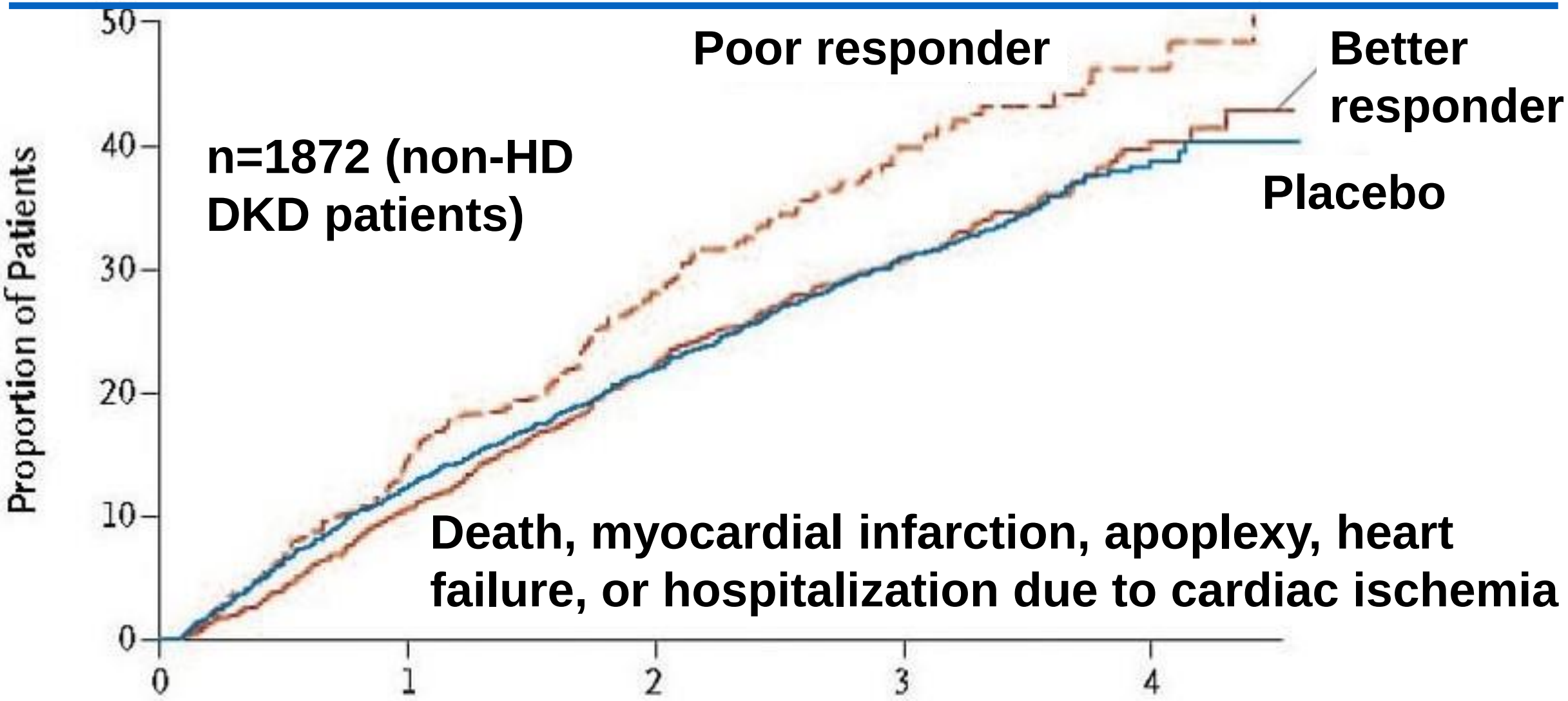
High Hb in patients treated with darbepoetin alfa is associated with better prognosis: a post-marketing surveillance in Japan

Composite renal endpoints: 50% reduction in eGFR, initiation of dialysis, or kidney transplantation



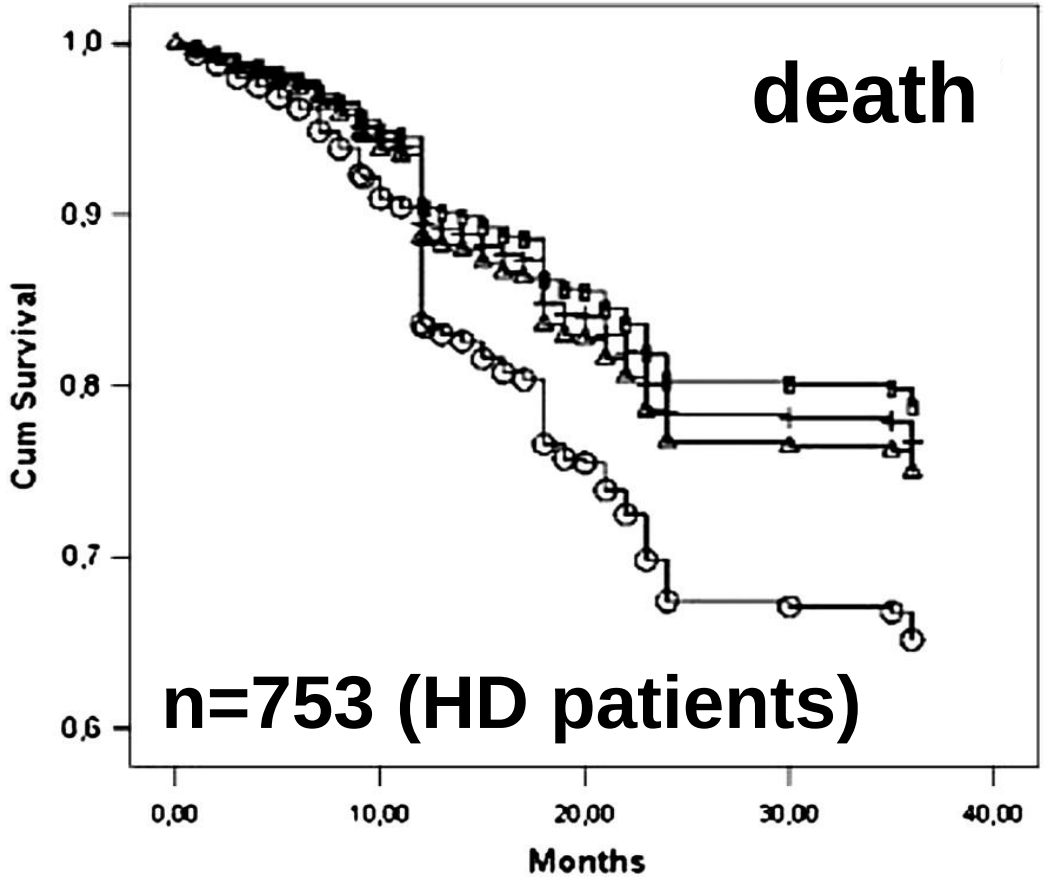
Tanaka, Nangaku et al. Clin Exp Nephrol 2019

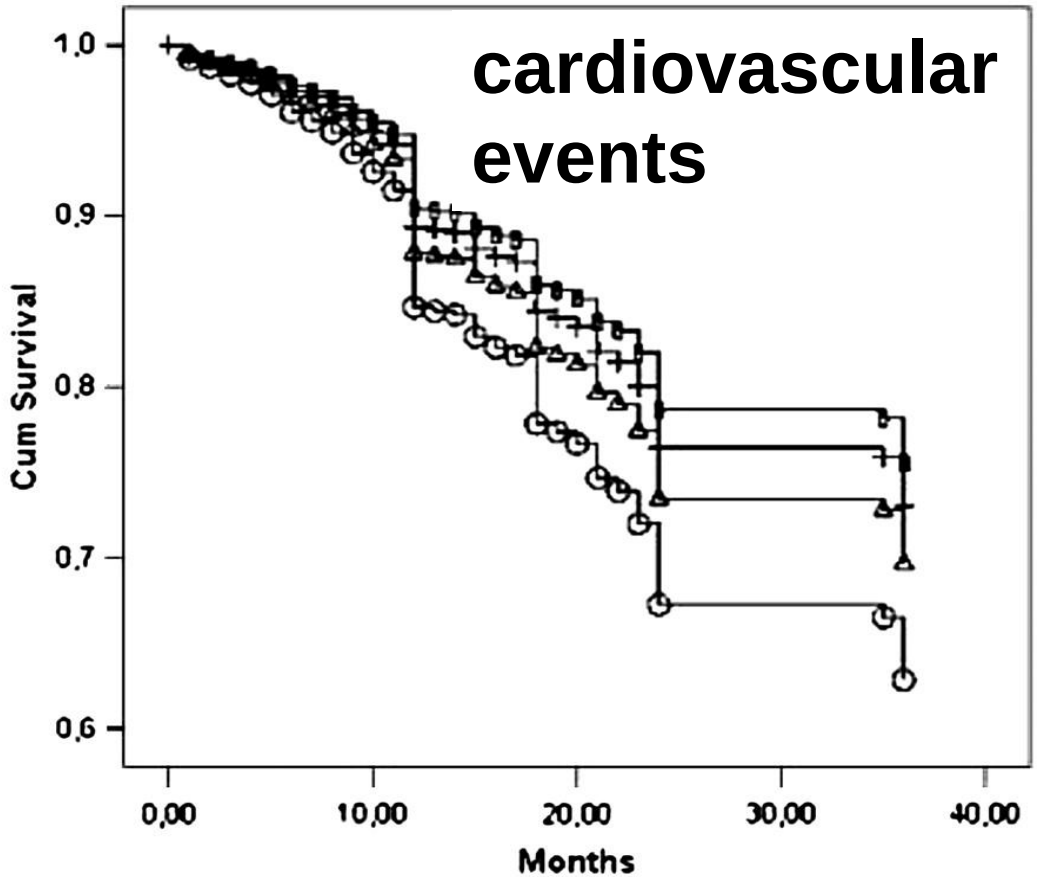
ESA hyporesponsiveness and poor outcome: TREAT study



Solomon et al. N Engl J Med 2010

ESA hyporesponsiveness and poor outcome: RISCAVID study





ESAs resistance index (ERI): the weekly ESAs dose / kgBW / Hb (g/dL)

Panichi et al. Nephrol Dial Transplant 2011

Erythropoietin hyporesponsiveness in Japanese HD patients: possible role of statins

a Association between statin prescription and subsequent ESA hyporesponsiveness by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Number of events, *n* (%)	OR (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
Hgb <10 g/dL	+	585	66 (11.3)	0.88 (0.67–1.13)	0.86 (0.65–1.14)	0.85 (0.64–1.13)	0.87 (0.66–1.15)
ESA dose[a] >6,000 units/week	–	3,017	394 (13.1)				

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.

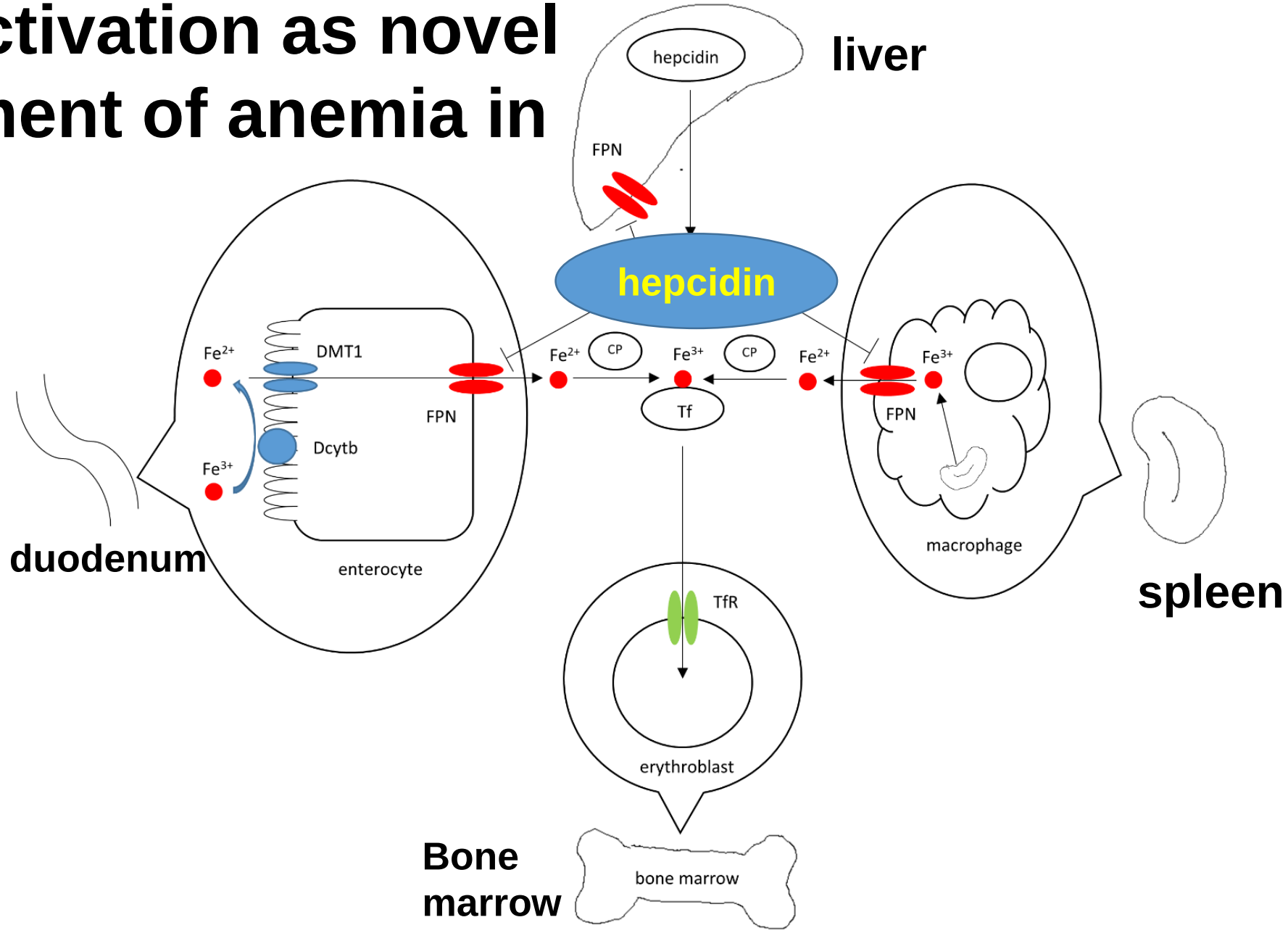
b Association between statin prescription and subsequent ESA resistance index by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Average ERI	Ratio of means (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
logERI[a,f]	+	585	10.1	0.92 (0.87–0.97)	0.95 (0.90–1.00)	0.94 (0.89–0.99)	0.94 (0.89–0.99)
	–	3,017	10.7				

ESA, erythropoiesis-stimulating agent; ERI, ESA resistance index.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.
[f] ERI = ESA/(dry weight × Hgb).

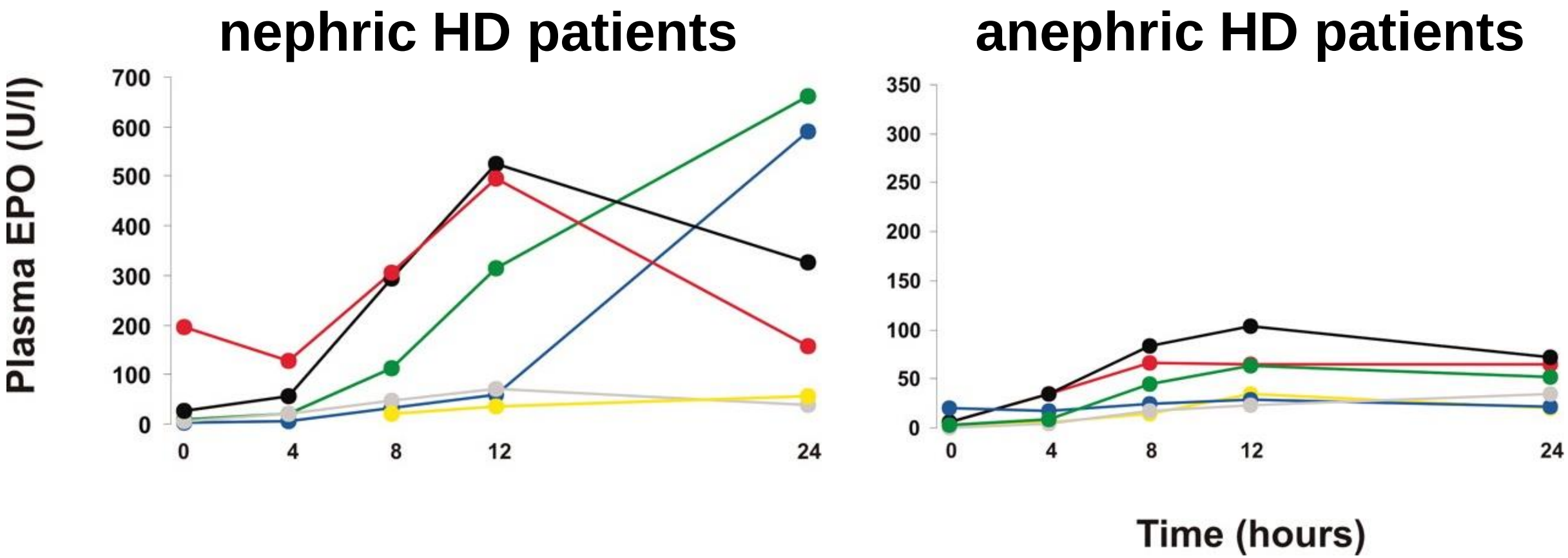
Hasegawa, Nangaku et al. Am J Nephrol 2017

HIF activation as novel treatment of anemia in CKD



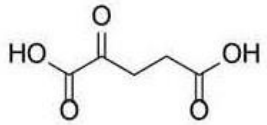
Sugahara, Tanaka T, Nangaku. Kidney Int 2017

HIF activator increases plasma-EPO levels in HD patients with and without remaining kidney

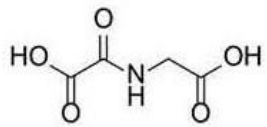


Bernhardt et al. JASN 2010

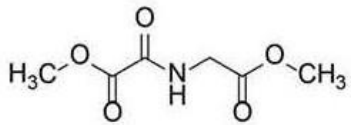
Chemical structures of HIF activators



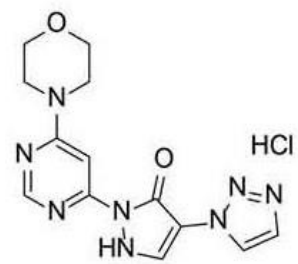
2OG



NOG

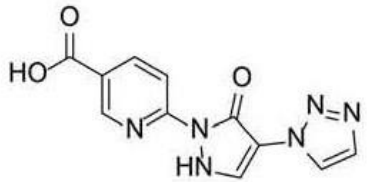


DMOG

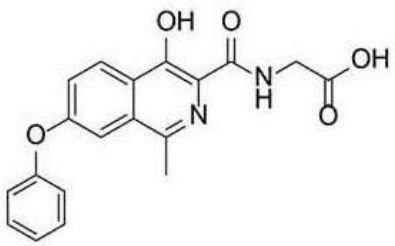


molidustat

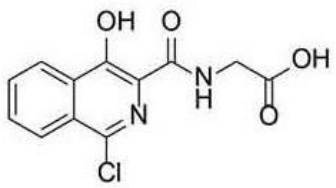
IOX4



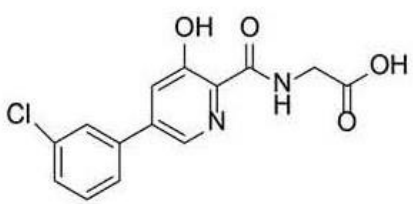
R8J



roxadustat

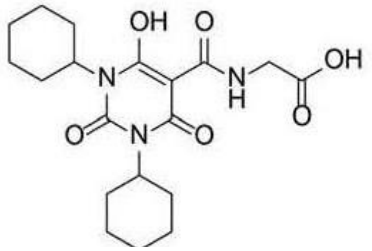


FG-2216

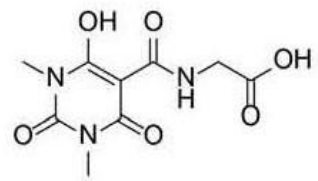


vadadustat

AKB-6899



daprodustat



CCT6

Yeh et al. Chem Sci 2017

Selectivity of HIF activators

all of the tested compounds are selective for PHD2 over FIH, and almost all of the tested JmjC domain containing histone demethylases (KDMs)

	IC_{50} [μM]									
Inhibitor	PHD2	FIH	Ofd1	Tpa1p	OGFOD1	JARID1A (KDM5A)	JARID1B (KDM5B)	JARID1C (KDM5C)	JARID1D (KDM5D)	JMJD3 (KDM6B)
roxadustat	0.027	>100	8.5	12.8	<1	>100	>100	>100	>100	>100
daprodustat	0.067	21	23.9	5.1	2.1	>100	>100	>100	>100	>100
molidustat	0.007	66	10.3	3.8	5.1	>100	>100	>100	>100	35
IOX4	0.003	31	41.3	2.3	<1	53	87	97	91	<1
vadadustat	0.029	29	ND[b]	ND[b]	1.4	>100	30	>100	>100	37

[a] Assay conditions are described in the Experimental and ESI sections and have been previously reported.[31,39,44,66] PHD2: HIF-prolyl hydroxylase-2, FIH: factor inhibiting HIF, OGFOD1: 2OG and iron-dependent oxygenase domain containing 1, Ofd1: 2OG and Fe(II) dioxygenase domain containing protein 1, Tpa1p: termination and polyadenylation protein 1, JARID1A (KDM5A): lysine-specific demethylase 5A, JARID1B (KDM5B): lysine-specific demethylase 5B JARID1C (KDM5C): lysine-specific demethylase 5C, JARID1D (KDM5D): lysine-specific demethylase 5D, JMJD3 (KDM6B): lysine-specific demethylase 6B. [b] ND, not determined.

Yeh et al. Chem Sci 2017

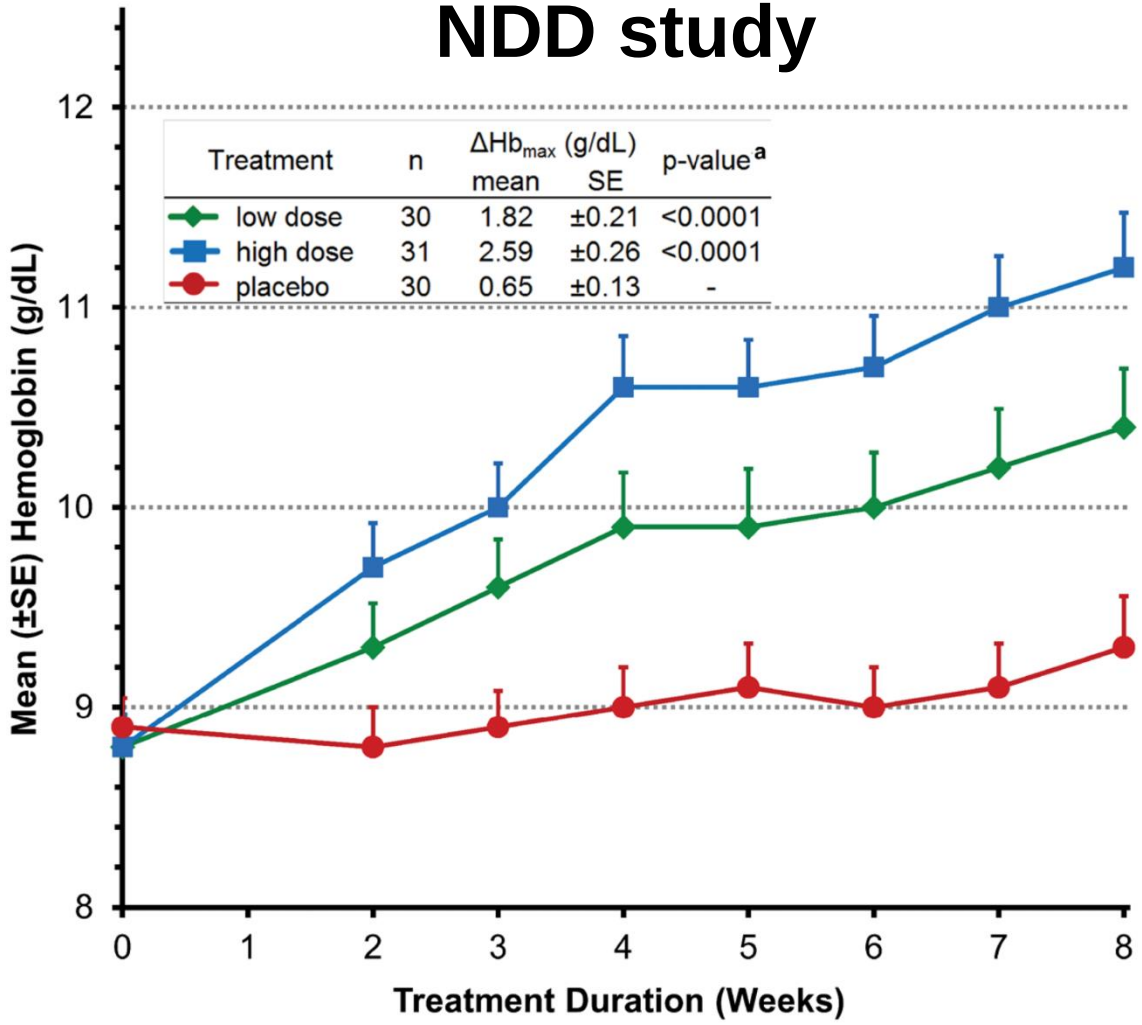
Clinical trials of PH inhibitors

	Non-dialysis CKD patients	Dialysis patients
Roxadustat	Alps, Olympus, Dolomites	Pyrenees, Himalayas, Sierras, Andes, Rockies
Vadadustat	PRO2TECT-CORRECTION/ CONVERSION	INNO2VATE - CORRECTION/ CONVERSION
Daprodustat	ASCEND-ND, ASCEND-NHQ	ASCEND-ID, ASCEND-D, ASCEND-TD
Molidustat	DIALOGUE 1 and 2, MIYABI-ND	DIALOGUE 4, MIYABI-HD
Enarodustat		

Improvement of anemia in CKD by HIF activator

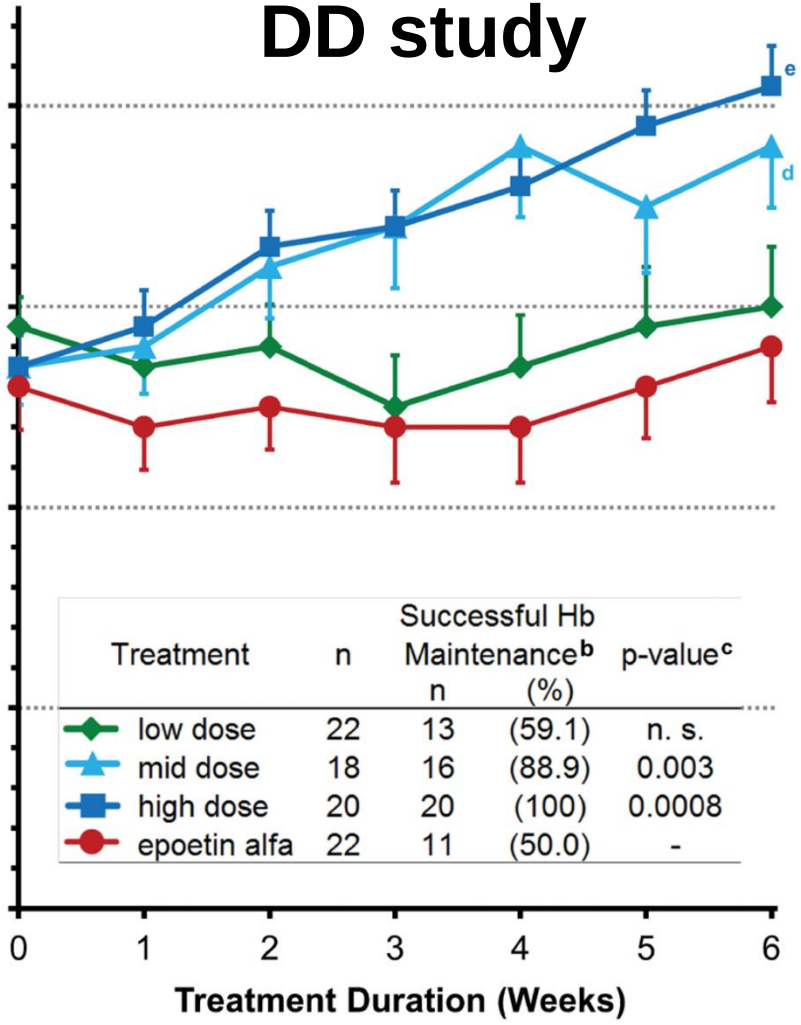
Phase 2 study of roxadustat in Chinese patients

NDD study



Treatment	n	ΔHb_{max} (g/dL) mean	SE	p-value[a]
low dose	30	1.82	±0.21	<0.0001
high dose	31	2.59	±0.26	<0.0001
placebo	30	0.65	±0.13	-

DD study



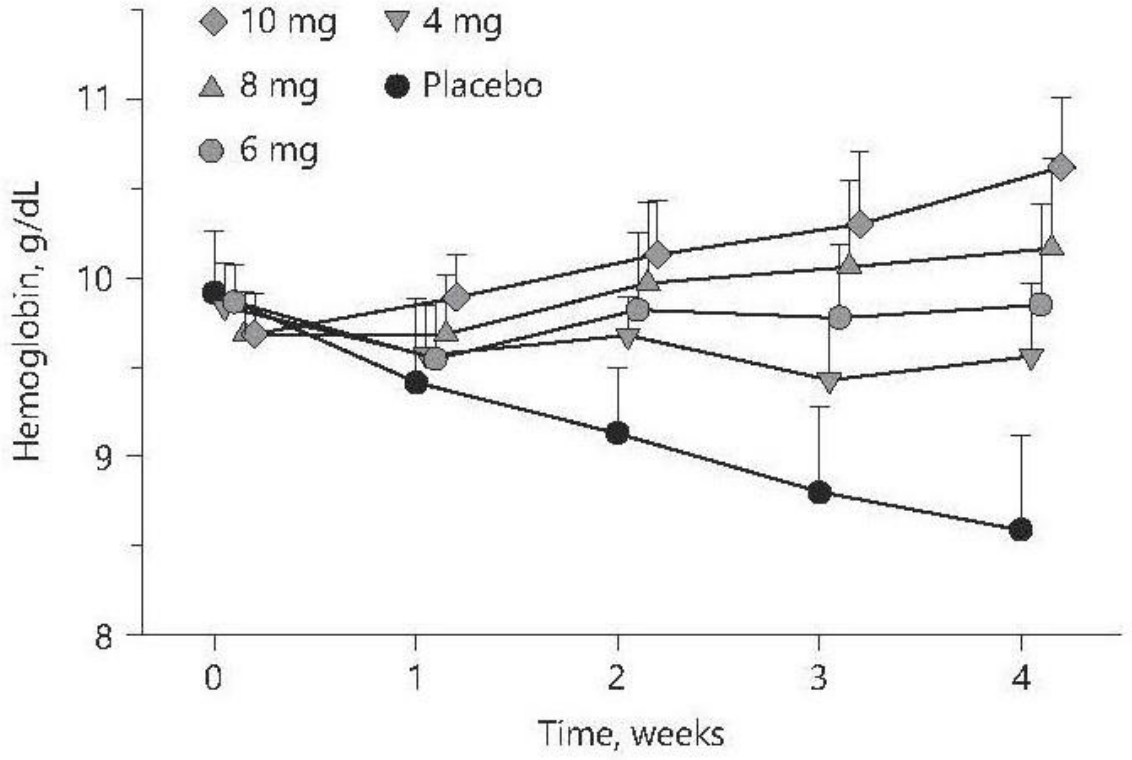
Treatment	n	Successful Hb Maintenance[b] n	(%)	p-value[c]
low dose	22	13	(59.1)	n. s.
mid dose	18	16	(88.9)	0.003
high dose	20	20	(100)	0.0008
epoetin alfa	22	11	(50.0)	-

Chen et al. NDT 2017

HIF activator improves anemia in CKD

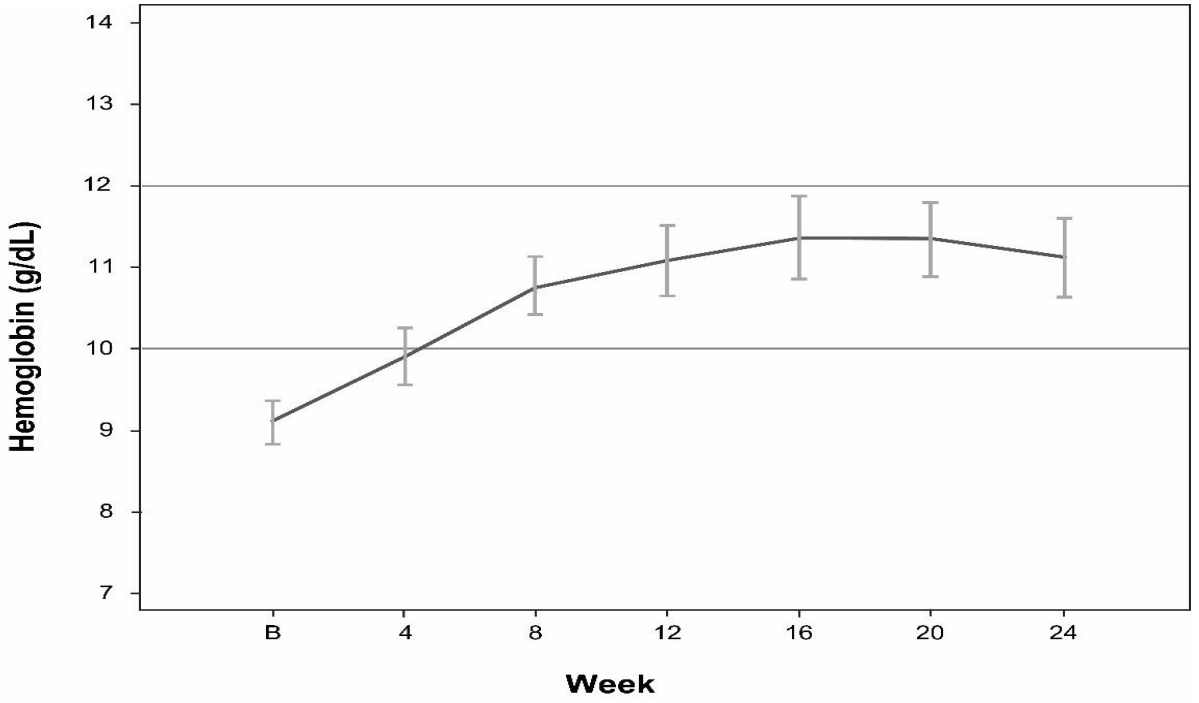
daprodustat in Japanese HD patients

phase 2



Akizawa, Nangaku et al.
Am J Nephrol 2017

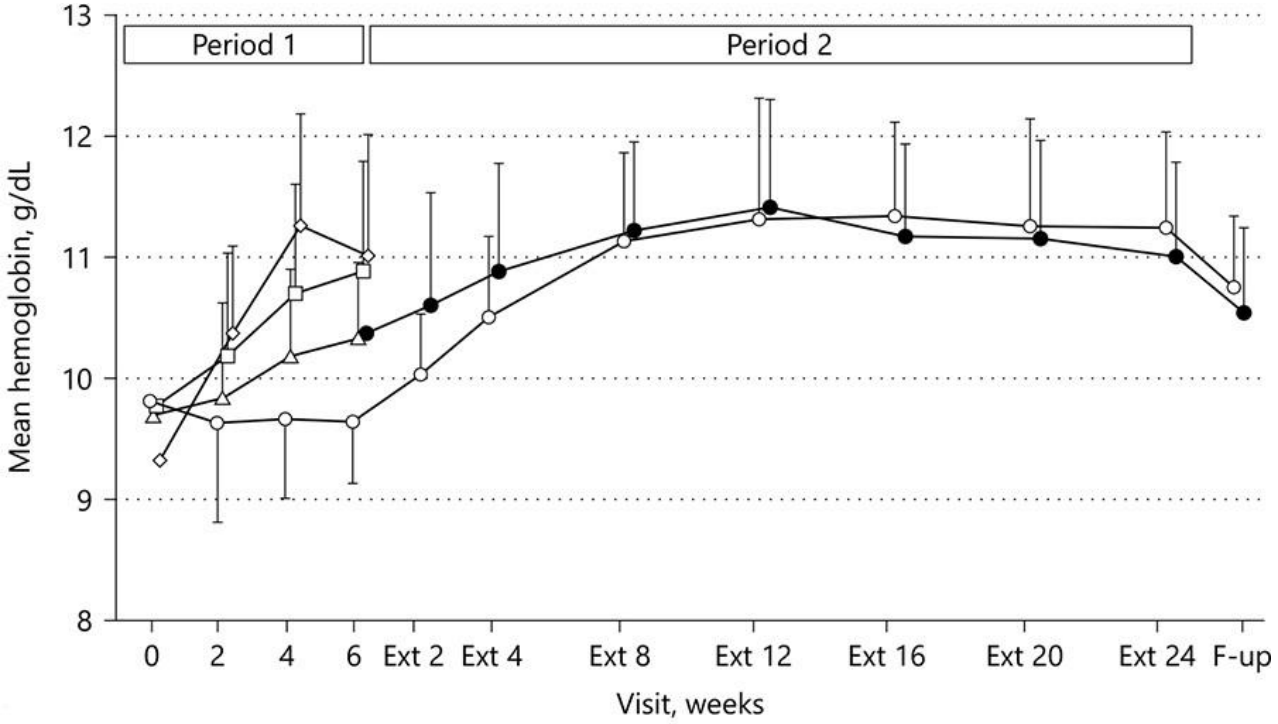
phase 3



Akizawa, Nangaku et al.
Ther Apher Dial 2019

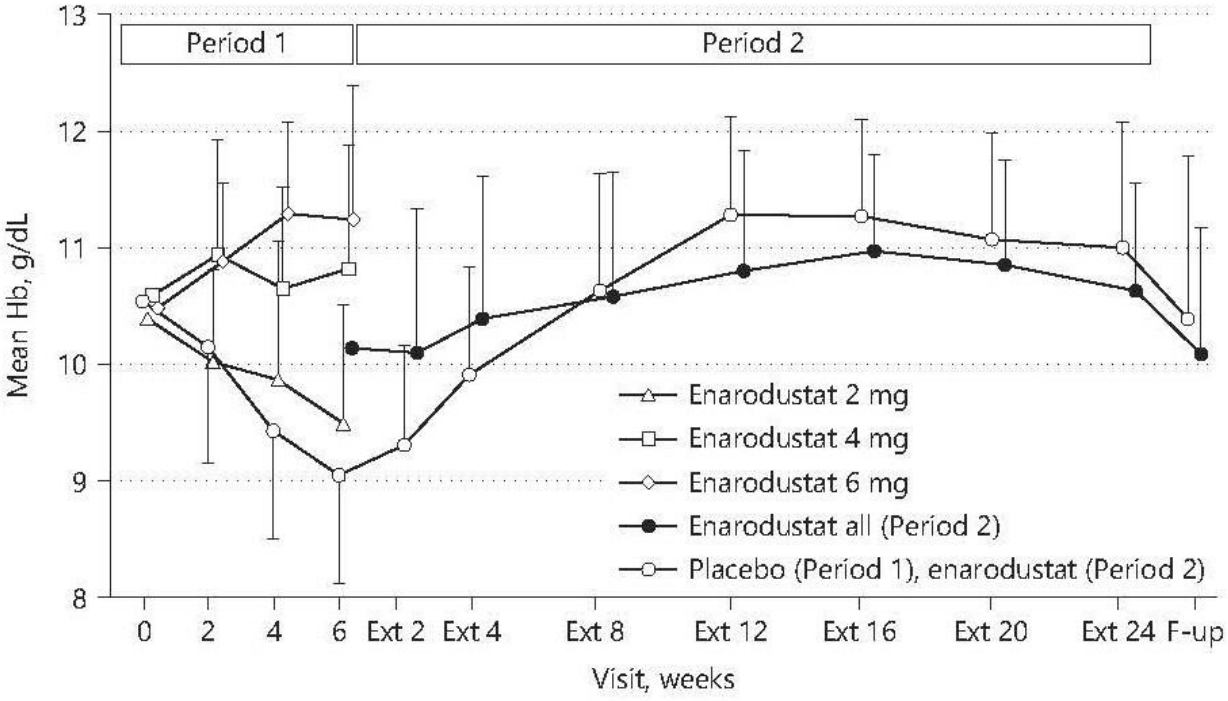
HIF activator improves anemia in CKD

enarodustat in Japanese non-HD patients



Akizawa, Nangaku et al.
Am J Nephrol 2019

enarodustat in Japanese HD patients



Akizawa, Nangaku et al.
Nephron 2019

decreases in the lipid parameters by roxadustat

	NDD study			DD study			
	Placebo	roxadustat low	roxadustat high	rhEPO	roxadustat low	roxadustat mid	roxadustat high
Total chol (mg/dL)	8.0 (±30.0)	-31.7 (±25.3)	-35.6 (±37.5)	18.3 (±24.32)	-11.1 (±31.31)	-13.1 (±31.64)	-15.8 (±48.63)
LDL-chol (mg/dL)	4 (±25.5)	-22.4 (±19.4)	-32.0 (±33.5)	-5.0 (±15.3)	-25.0 (±20.2)	-23.4 (±20.6)	-25.8 (±27.6)

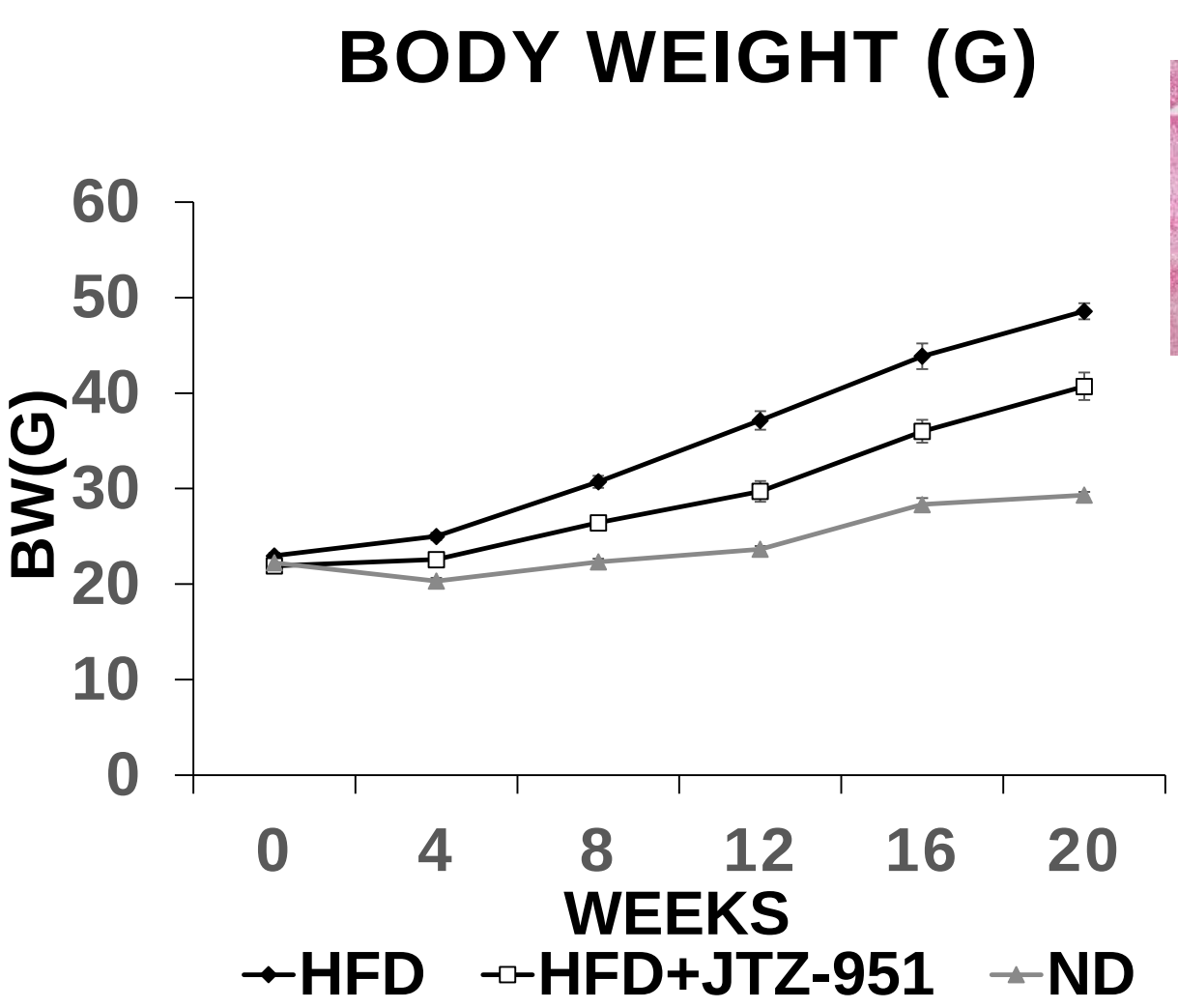
Chen et al. NDT 2017

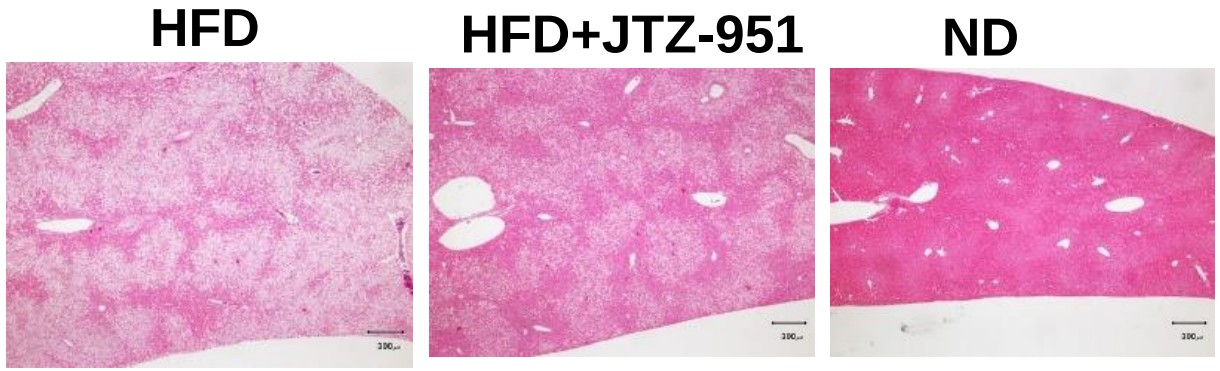
decreases in the lipid parameters by daprodustat

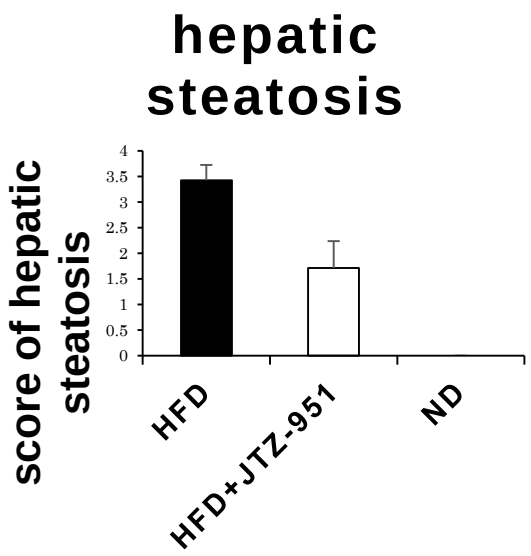
		Placebo	Daprodustat			
			4 mg	6 mg	8 mg	10 mg
Total Chol (mmol/L)	Baseline 95% CI	3.8 (3.5, 4.2)	4.0 (3.7, 4.5)	3.9 (3.6, 4.4)	3.7 (3.3, 4.2)	3.9 (3.6, 4.2)
	Week 4 CFB 95% CI	5.3 (-0.6, 11.6)	-7.4 (-12.2, -2.3)	-10.8 (-15.3, -6.0)	-9.0 (-14.9, -2.7)	-14.6 (-19.8, -9.0)
LDL-C (mmol/L)	Baseline 95% CI	2.0 (1.7, 2.3)	2.2 (1.9, 2.5)	2.1 (1.8, 2.4)	1.9 (1.6, 2.3)	2.1 (1.8, 2.4)
	Week 4 CFB 95% CI	4.8 (-10.4, 22.5)	-11.1 (-17.2, -4.7)	-10.8 (-17.2, -4.0)	-12.5 (-18.8, -5.7)	-17.3 (-24.3, -9.6)

Akizawa, Nangaku et al. Am J Nephrol 2017

HIF activation improved obesity and fatty liver in mice fed with high fat diet

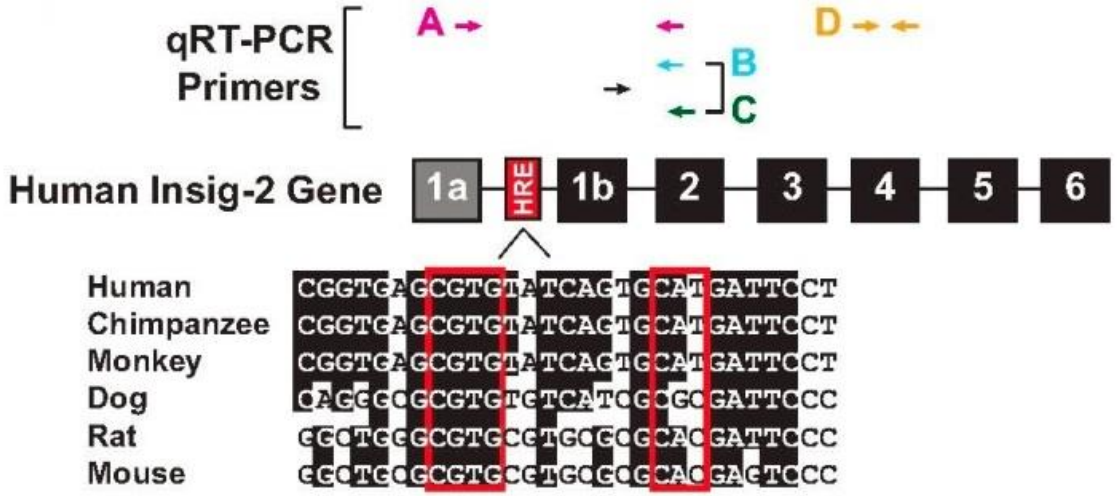


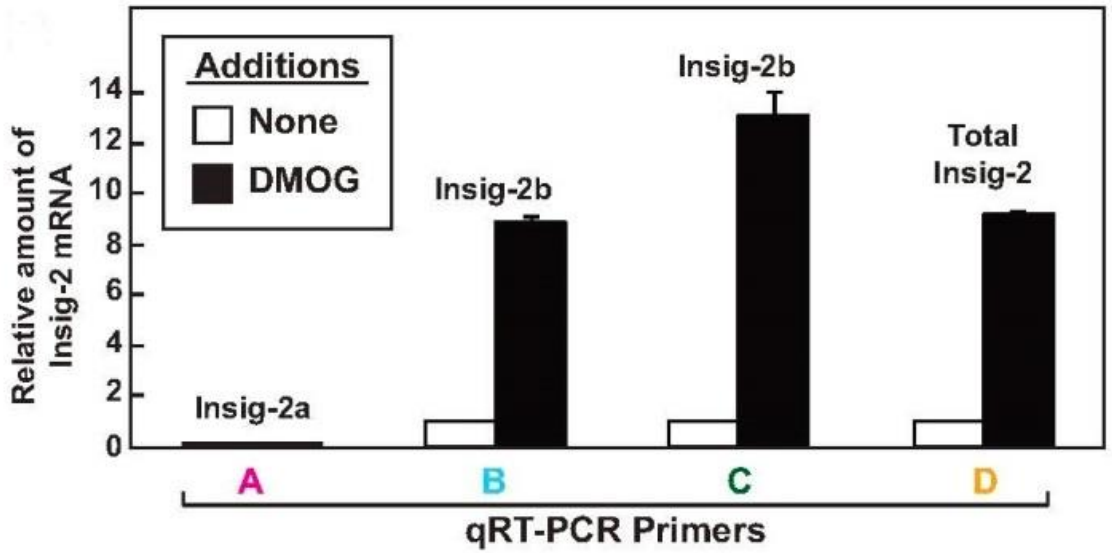


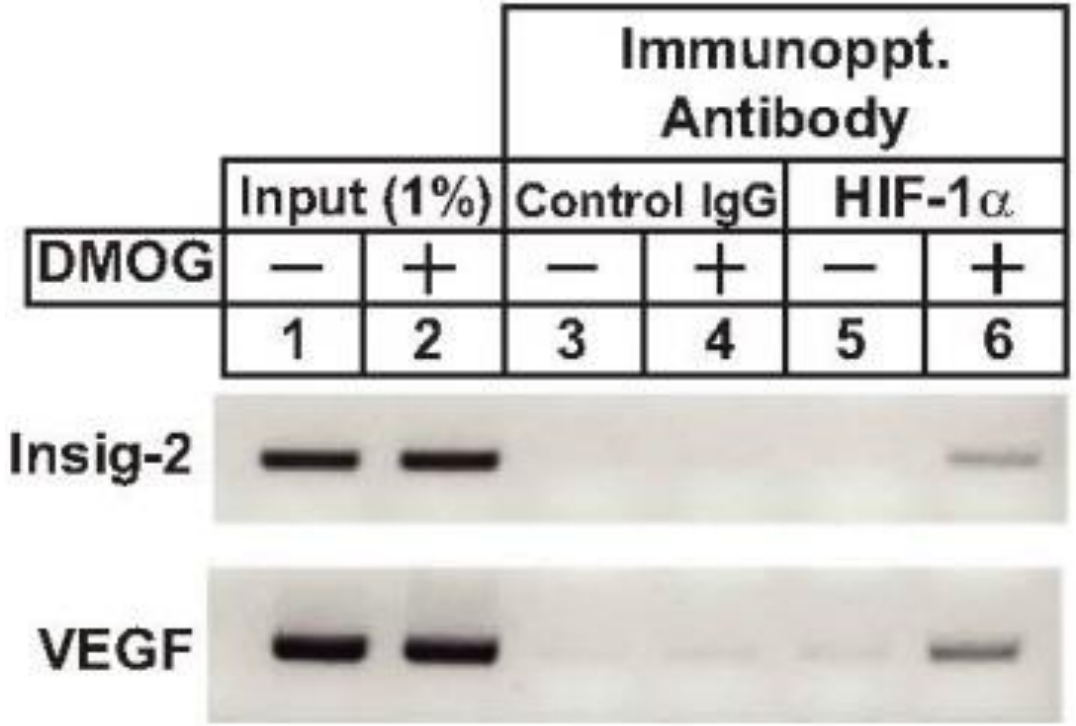


Saito, Nangaku et al. Lab Invest 2019

HIF-1 activates insulin-induced gene 2 (Insig-2) transcription

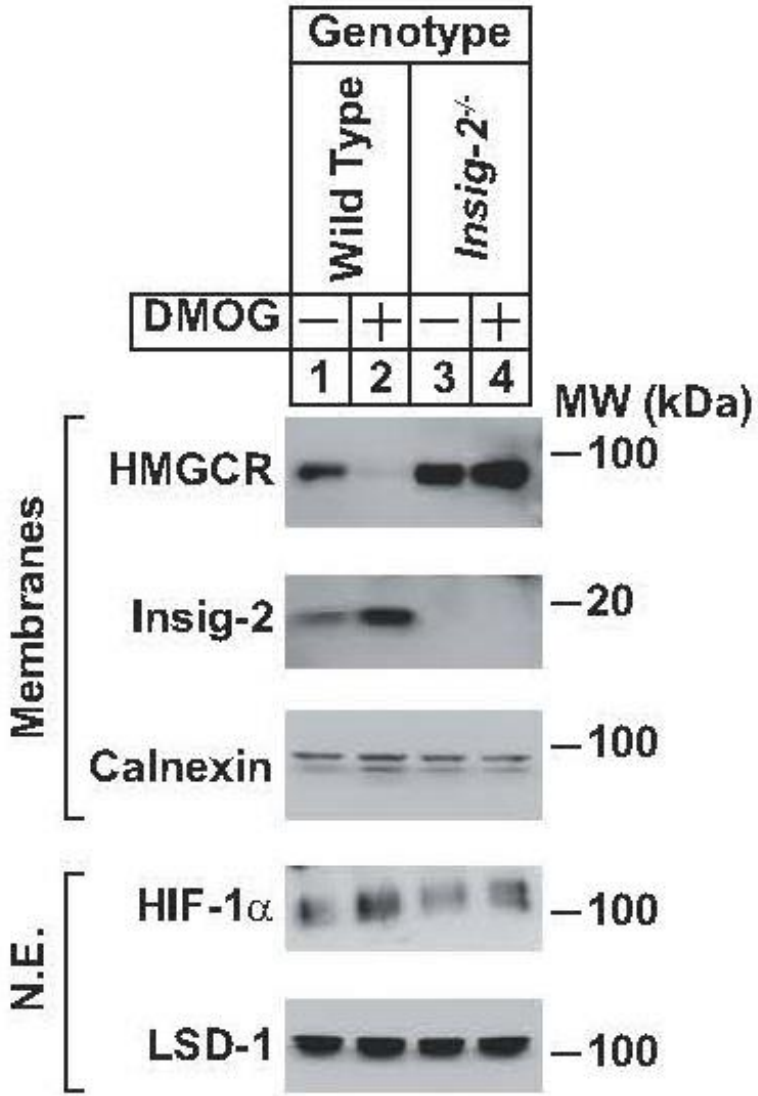


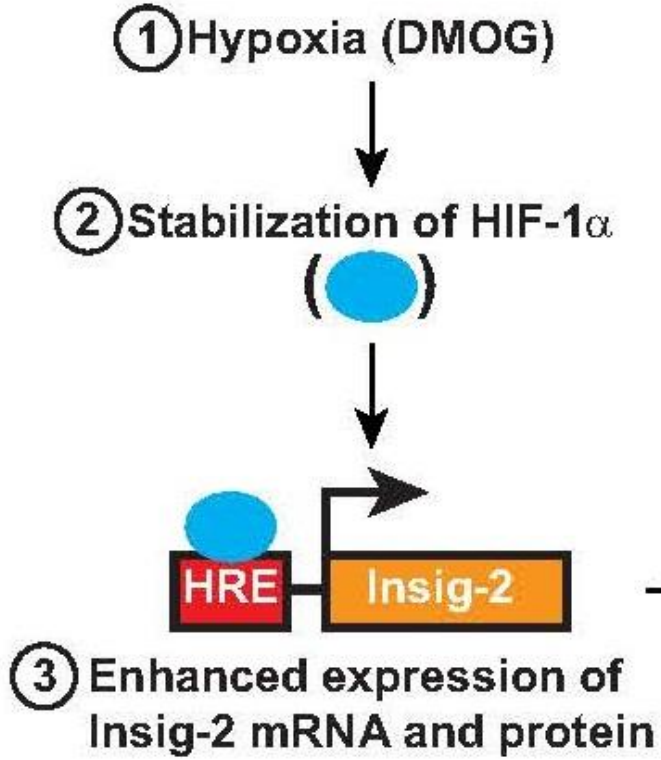


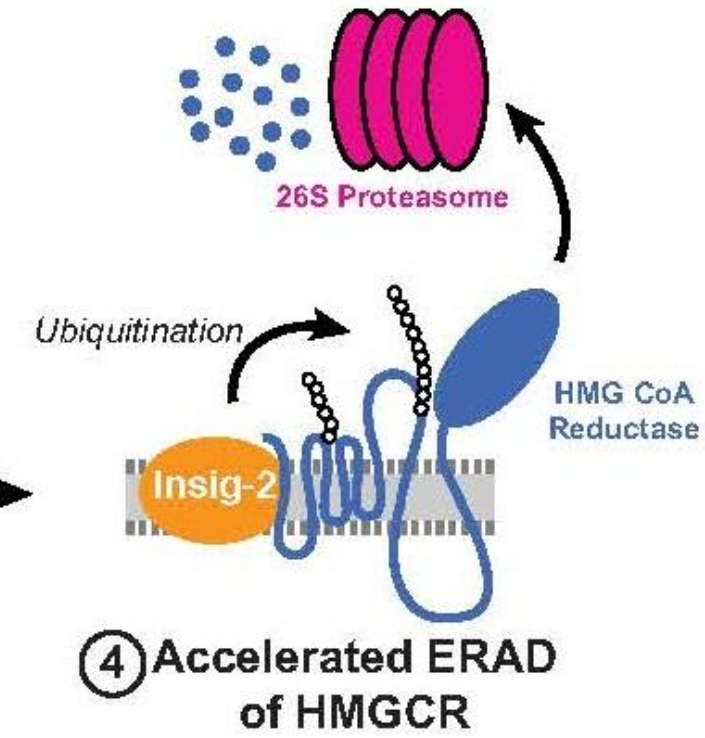


Hwang et al. J Biol Chem 2017

HIF-1 activates Insig-2 transcription for degradation of HMG-CoA reductase in the liver



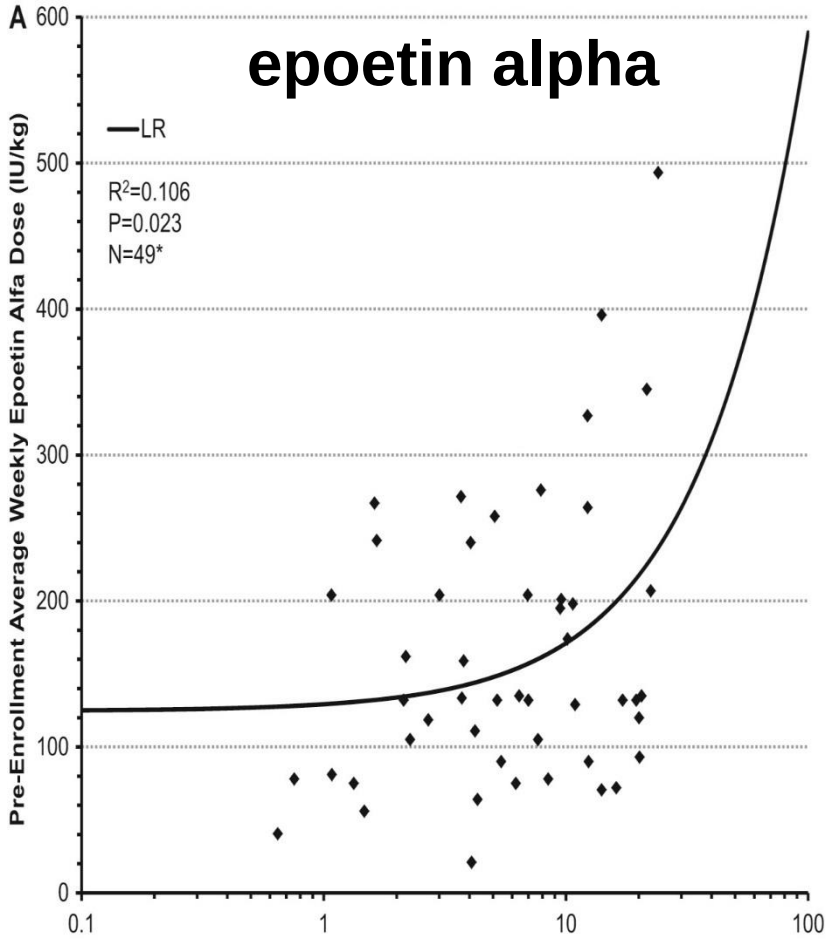


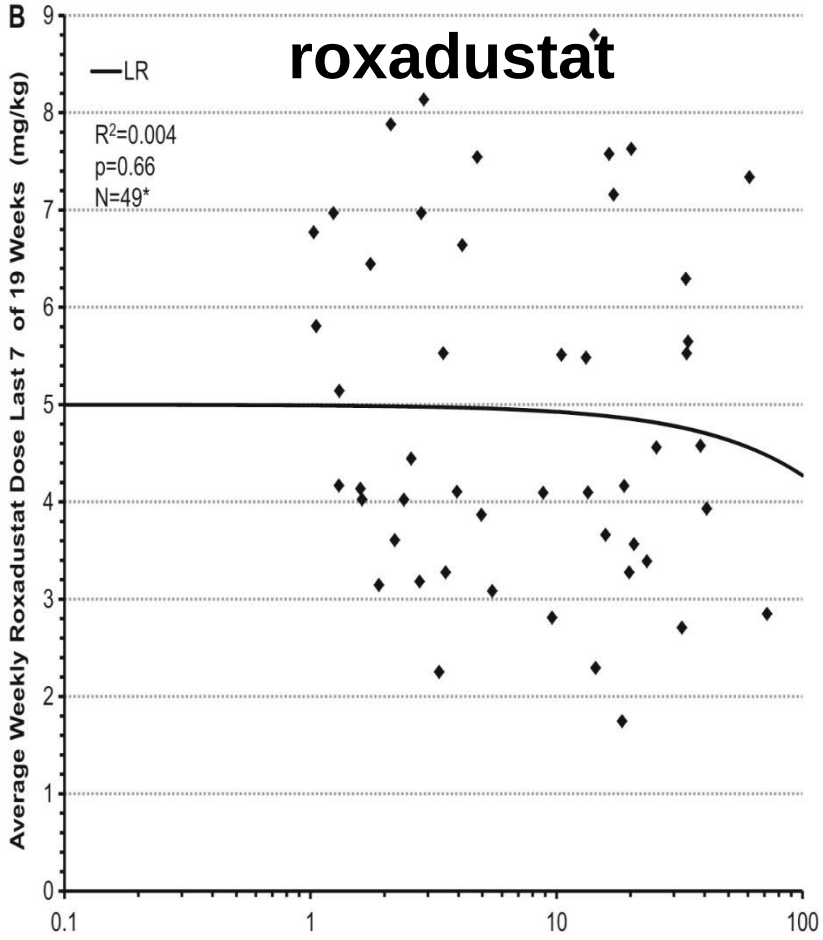


Hwang et al. J Biol Chem 2017

roxadustat maintenance dose requirements were independent of baseline CRP levels

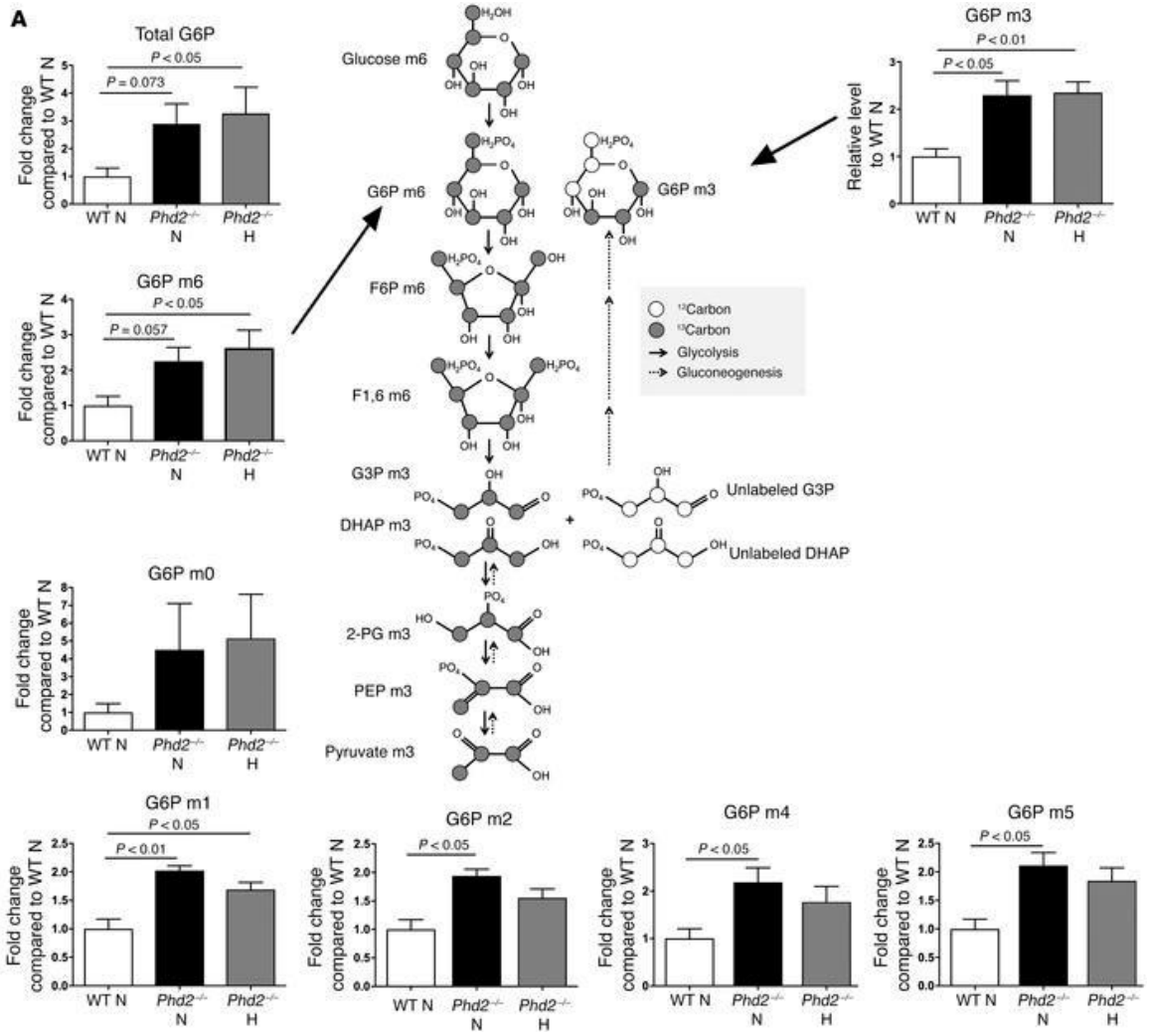
efficacy in ESA hyporesponsive patients ?

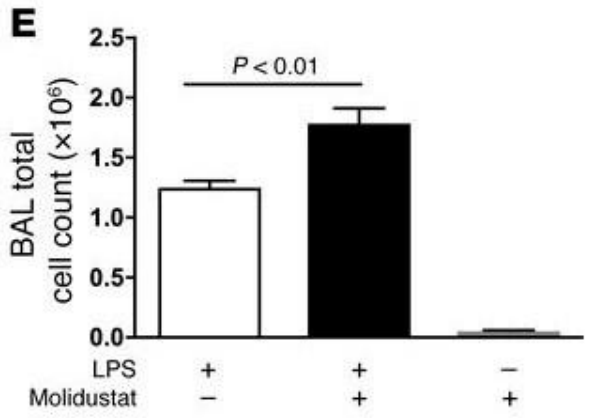


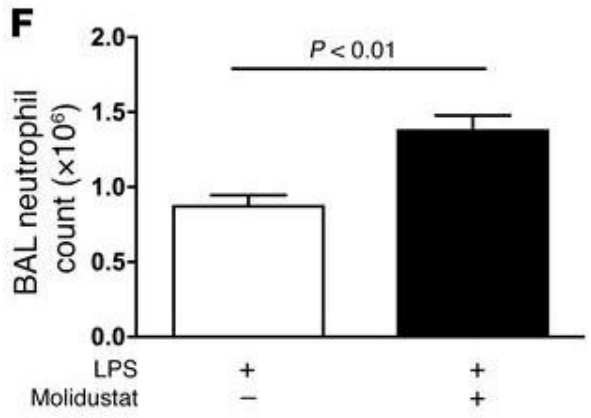


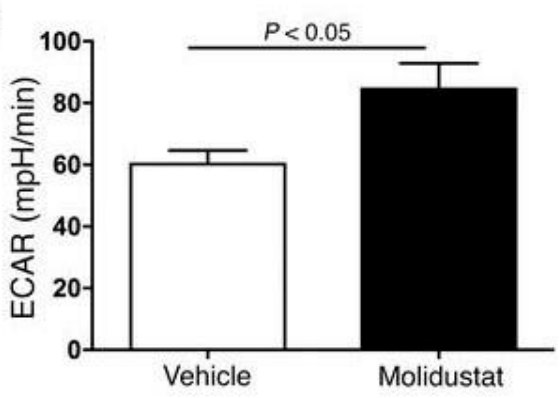
Provenzano et al. AJKD 2016

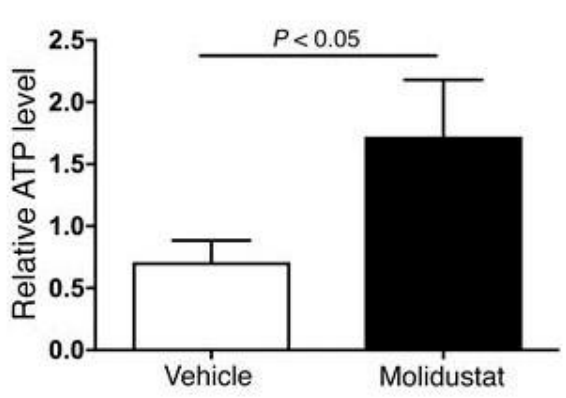
Metabolic reprogramming of neutrophils by Phd2 knockout augmented inflammation





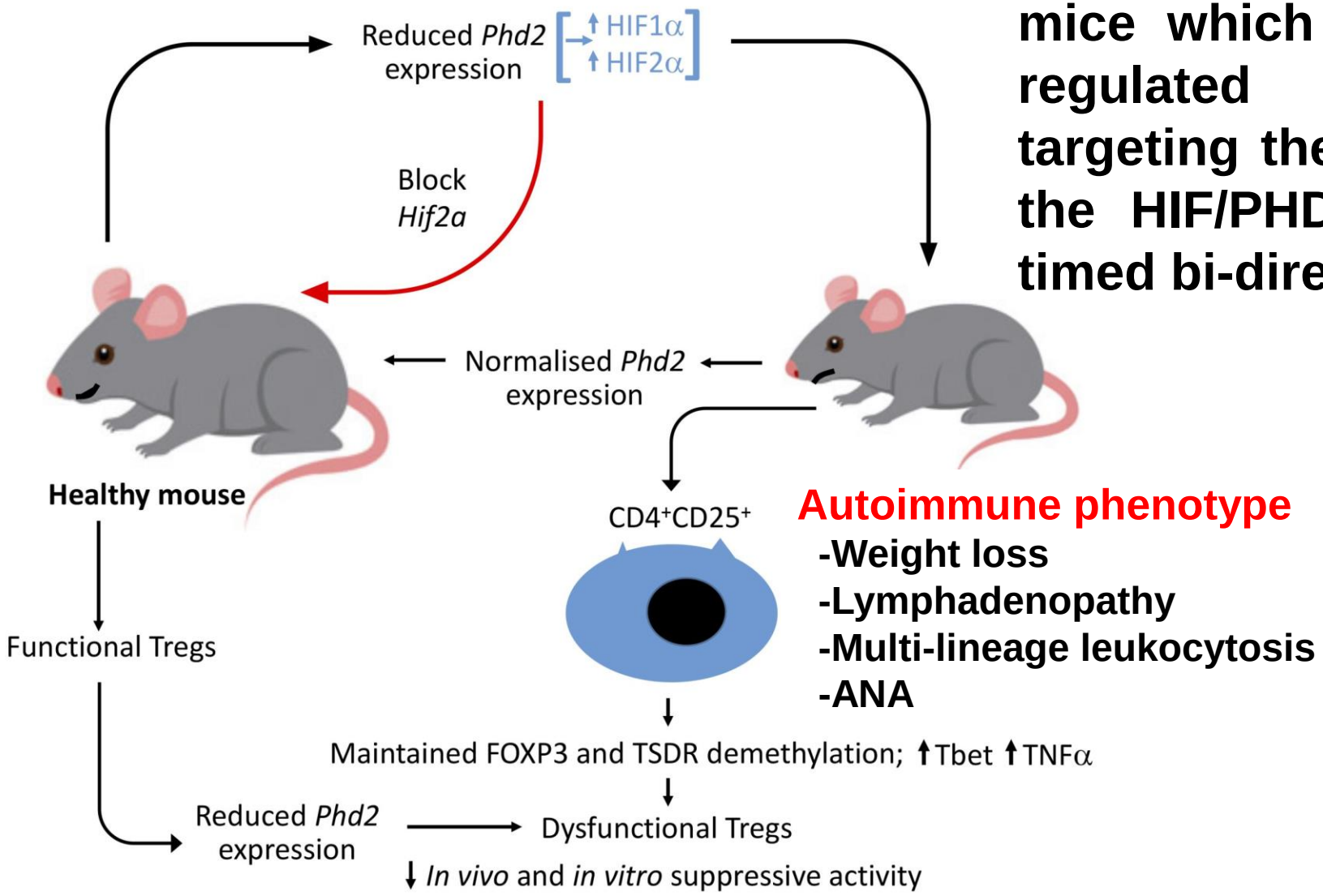






Sadiku et al.
J Clin Invest 2017

Systemic silencing of PHD2 causes reversible immune regulatory dysfunction



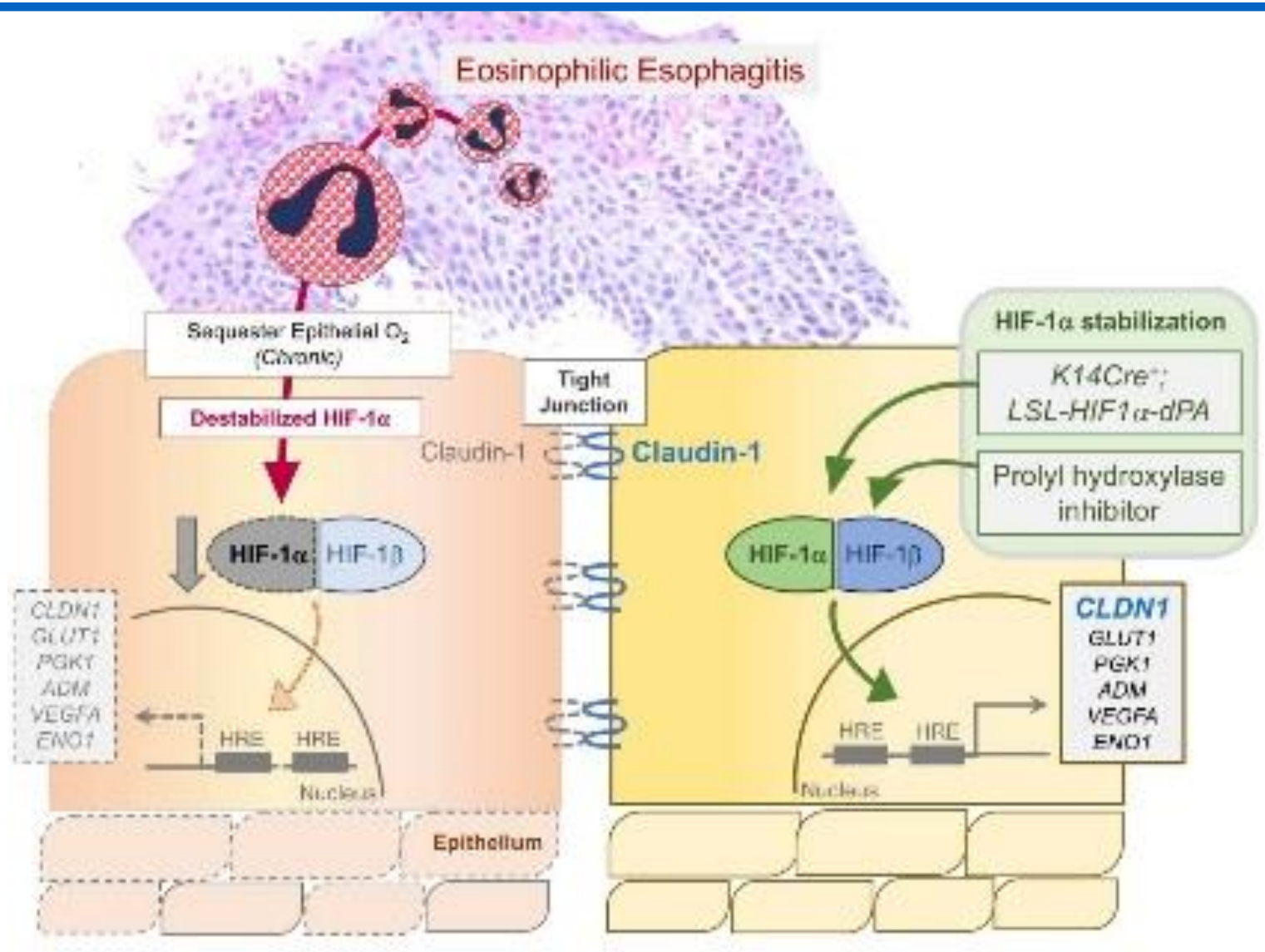
mice which express tetracycline-regulated shRNAs broadly targeting the main components of the HIF/PHD pathway, permitting timed bi-directional intervention

Autoimmune phenotype

- **Weight loss**
- **Lymphadenopathy**
- **Multi-lineage leukocytosis**
- **ANA**

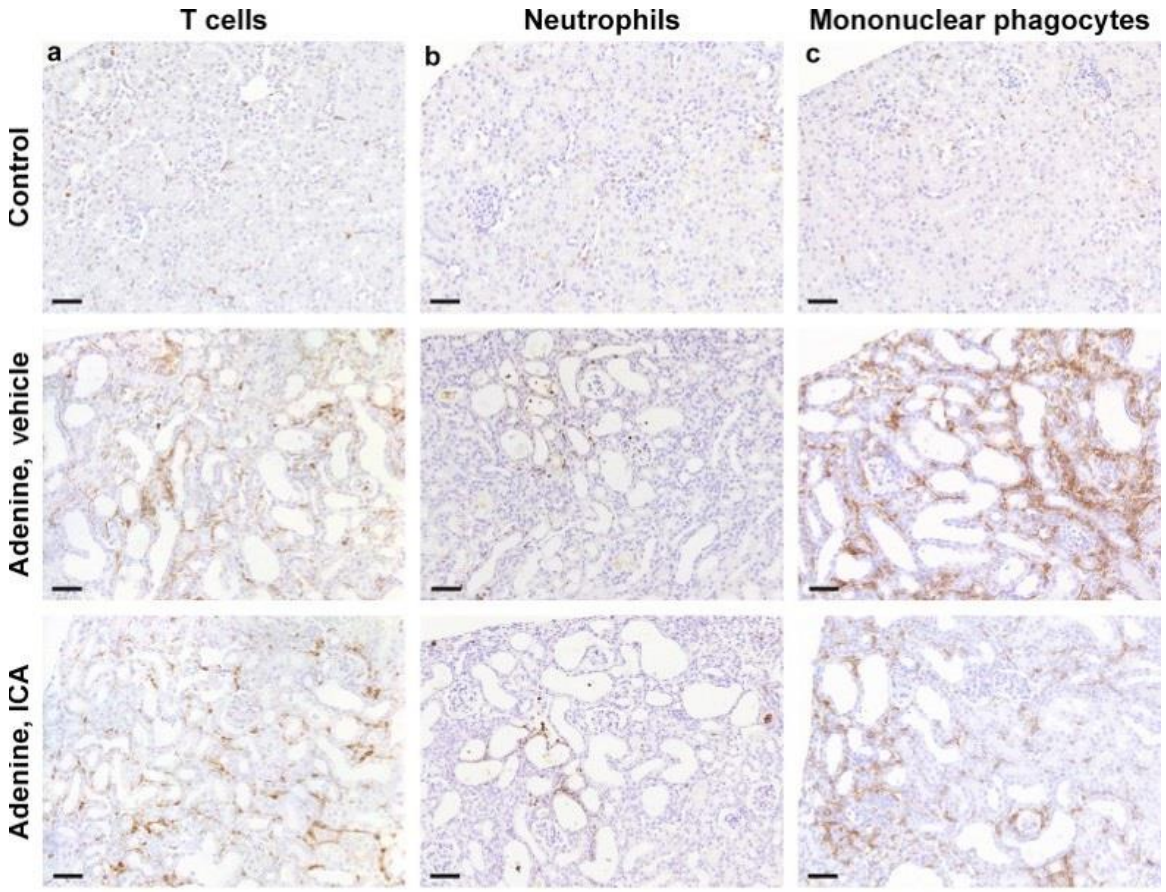
Yamamoto et al.
J Clin Invest 2019

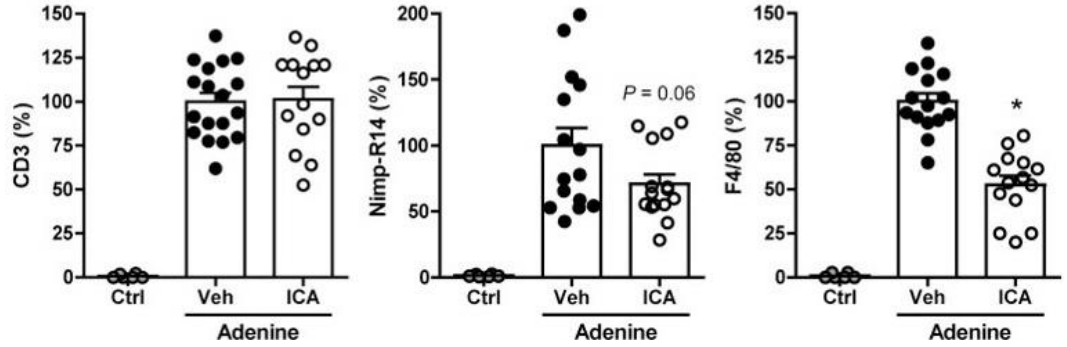
Epithelial HIF-1α/claudin-1 axis regulates barrier dysfunction in eosinophilic esophagitis

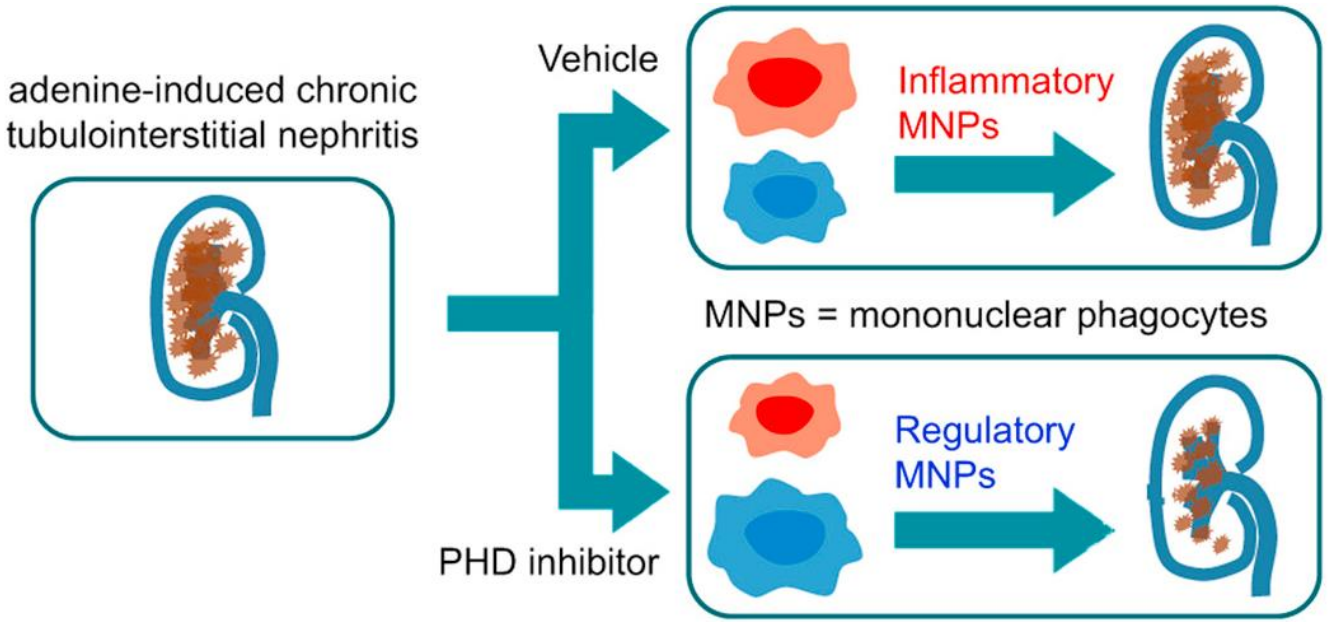


Masterson et al.
J Clin Invest 2019

Renoprotection by HIF activator by anti-inflammatory response in a model of tubulointerstitial nephritis

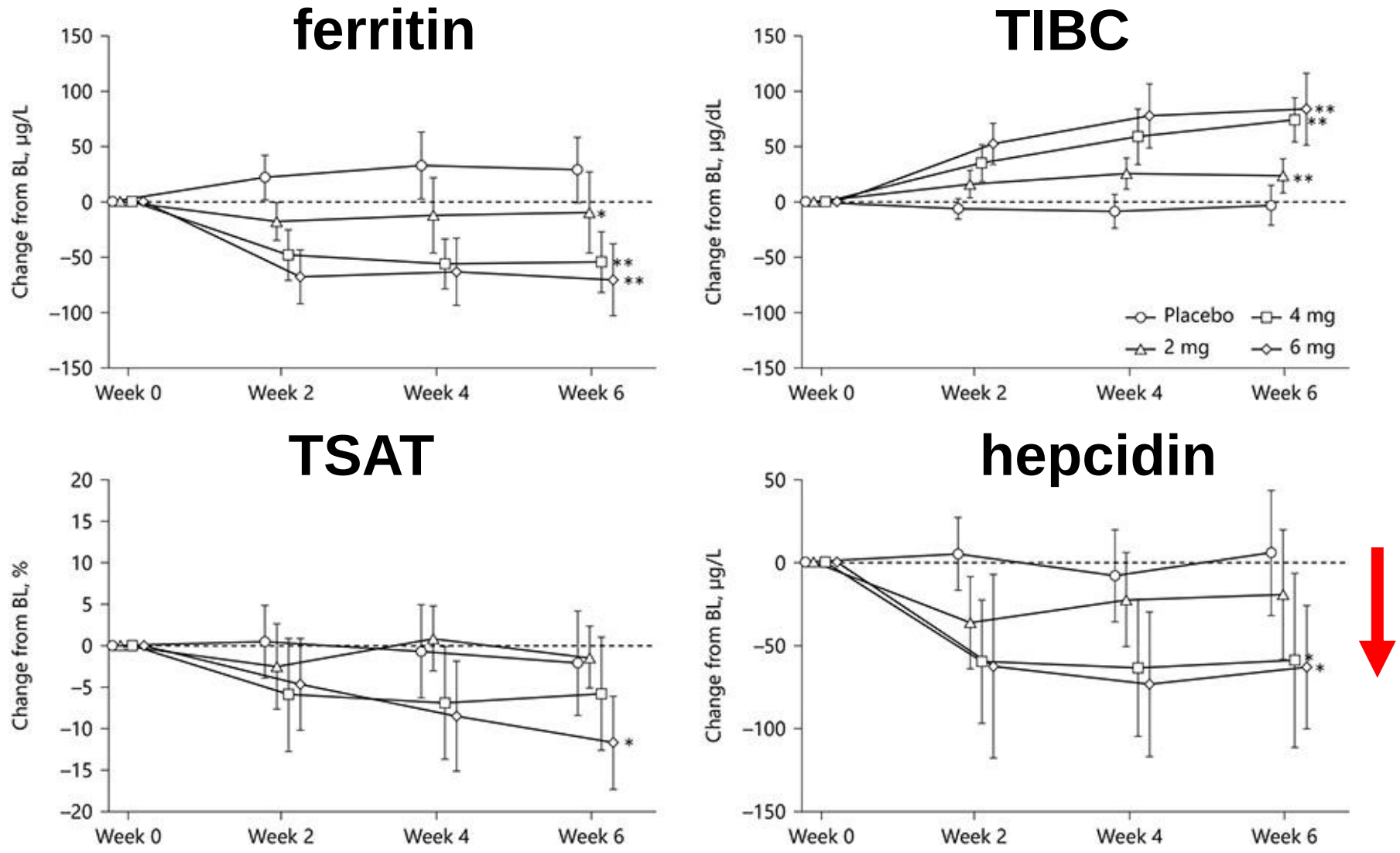






Schley et al. Kidney Int 2019

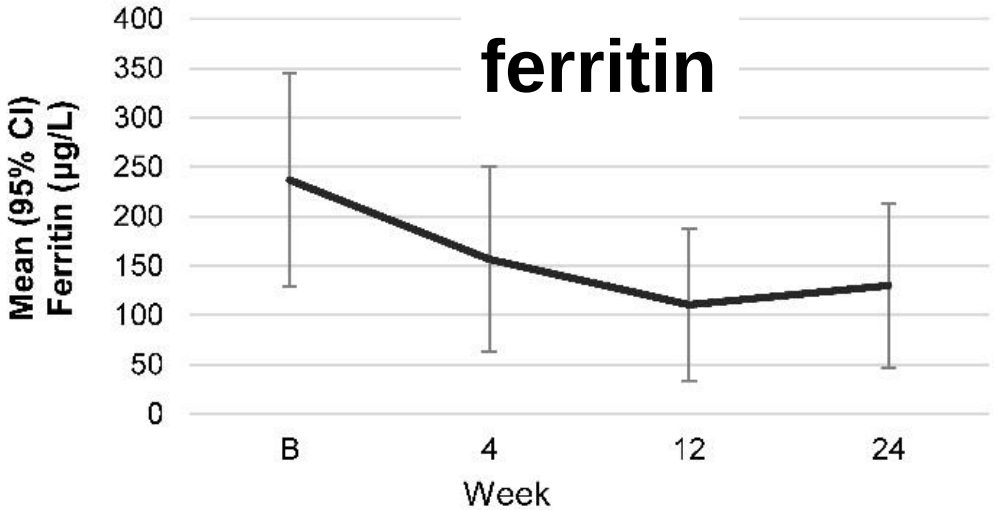
Changes of iron status: enarodustat

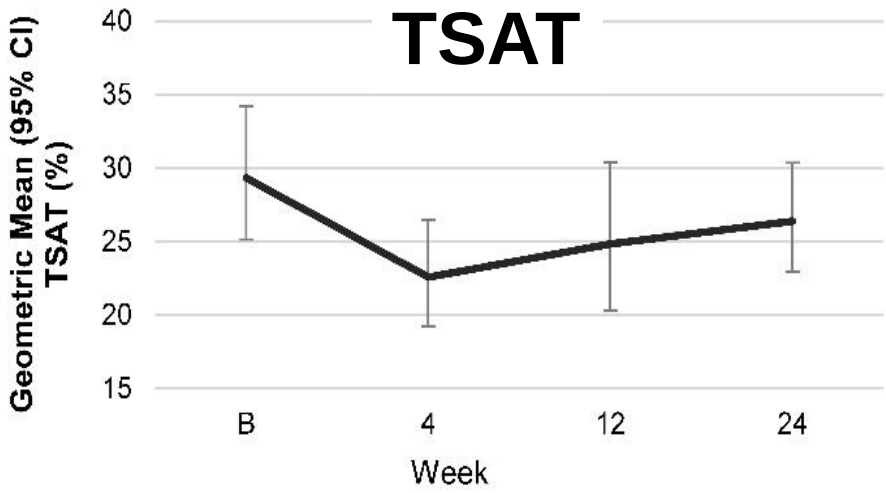


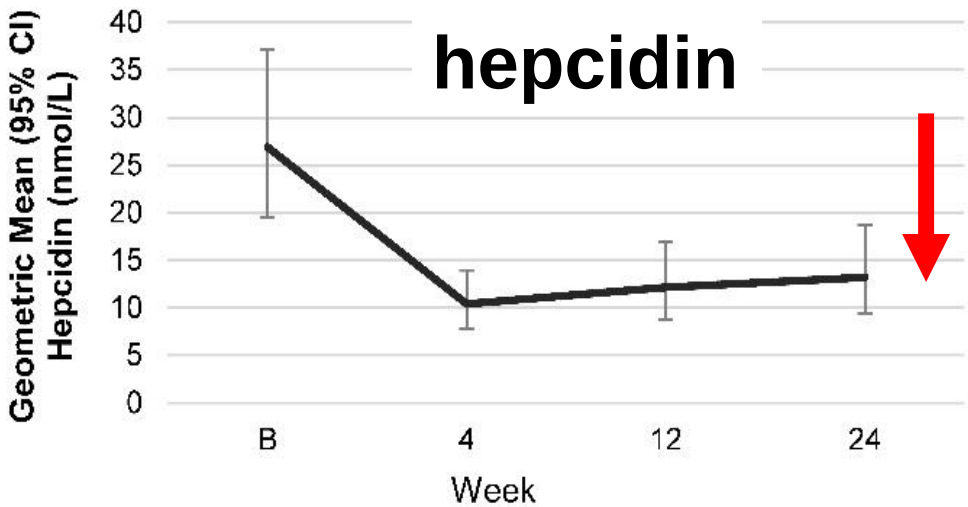
Akizawa, Nangaku et al. Am J Nephrol 2019

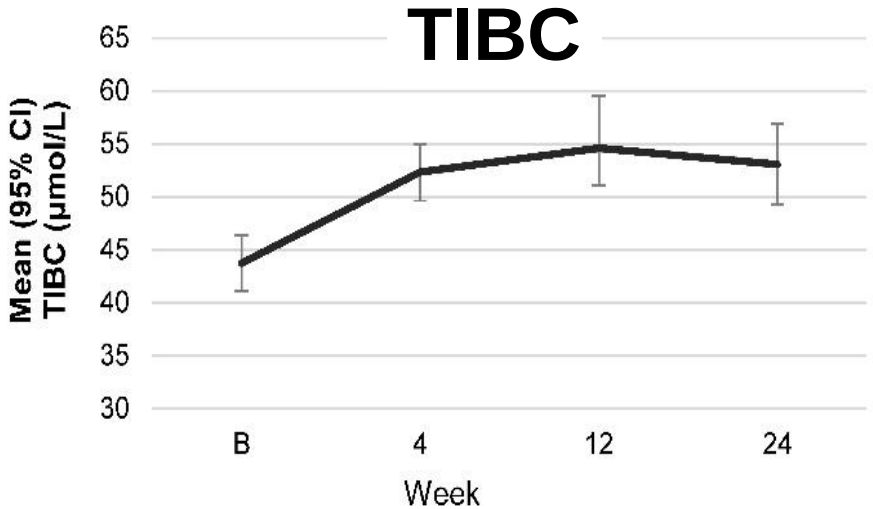
Changes of iron status: daprodustat

phase 3 study in Japanese HD patients



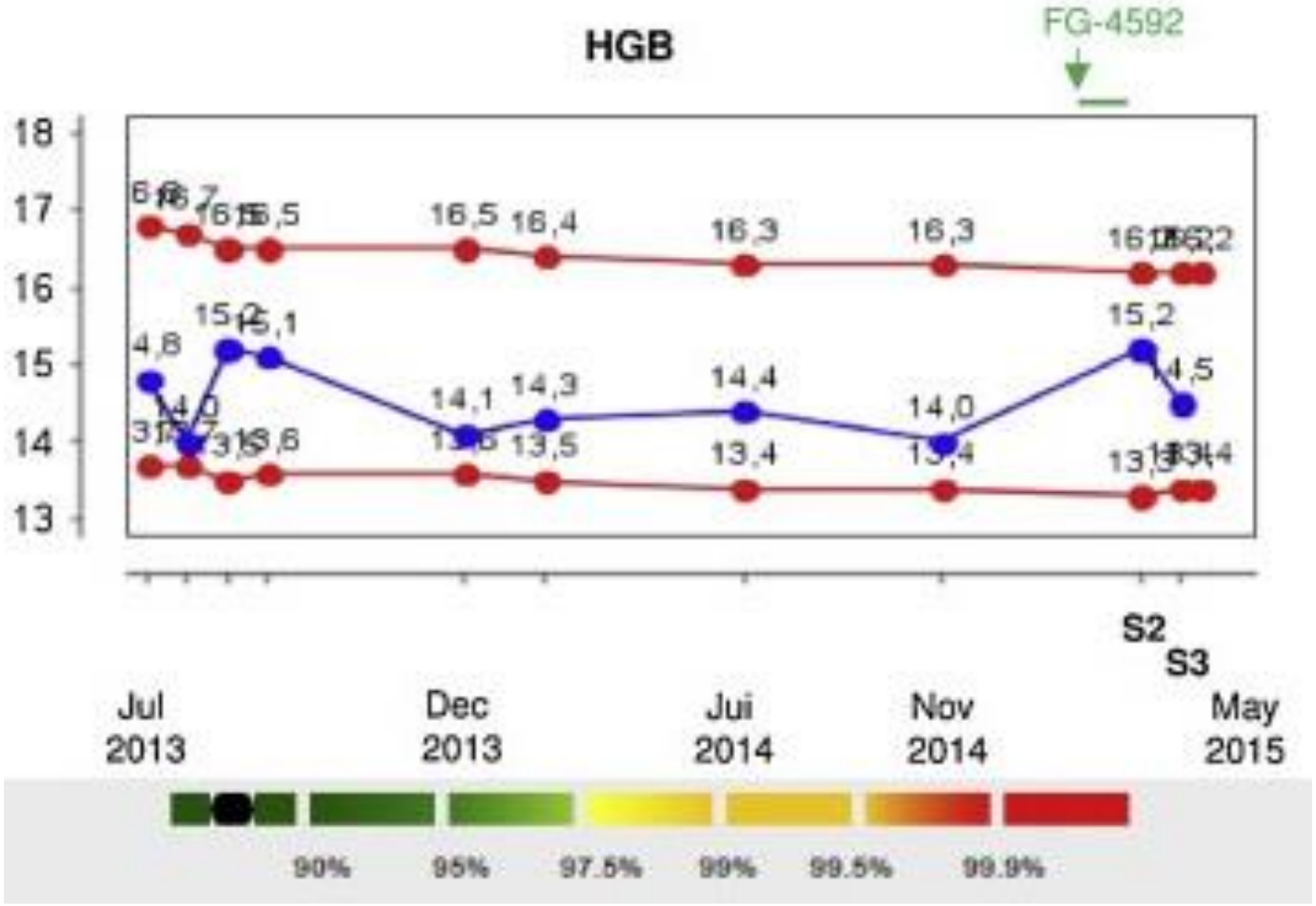






Akizawa, Nangaku et al. Ther Apher Dial 2019

first case of doping with HIF activator, FG-4592



Buisson et al. J Pharm Biomed Anal 2016

Research article

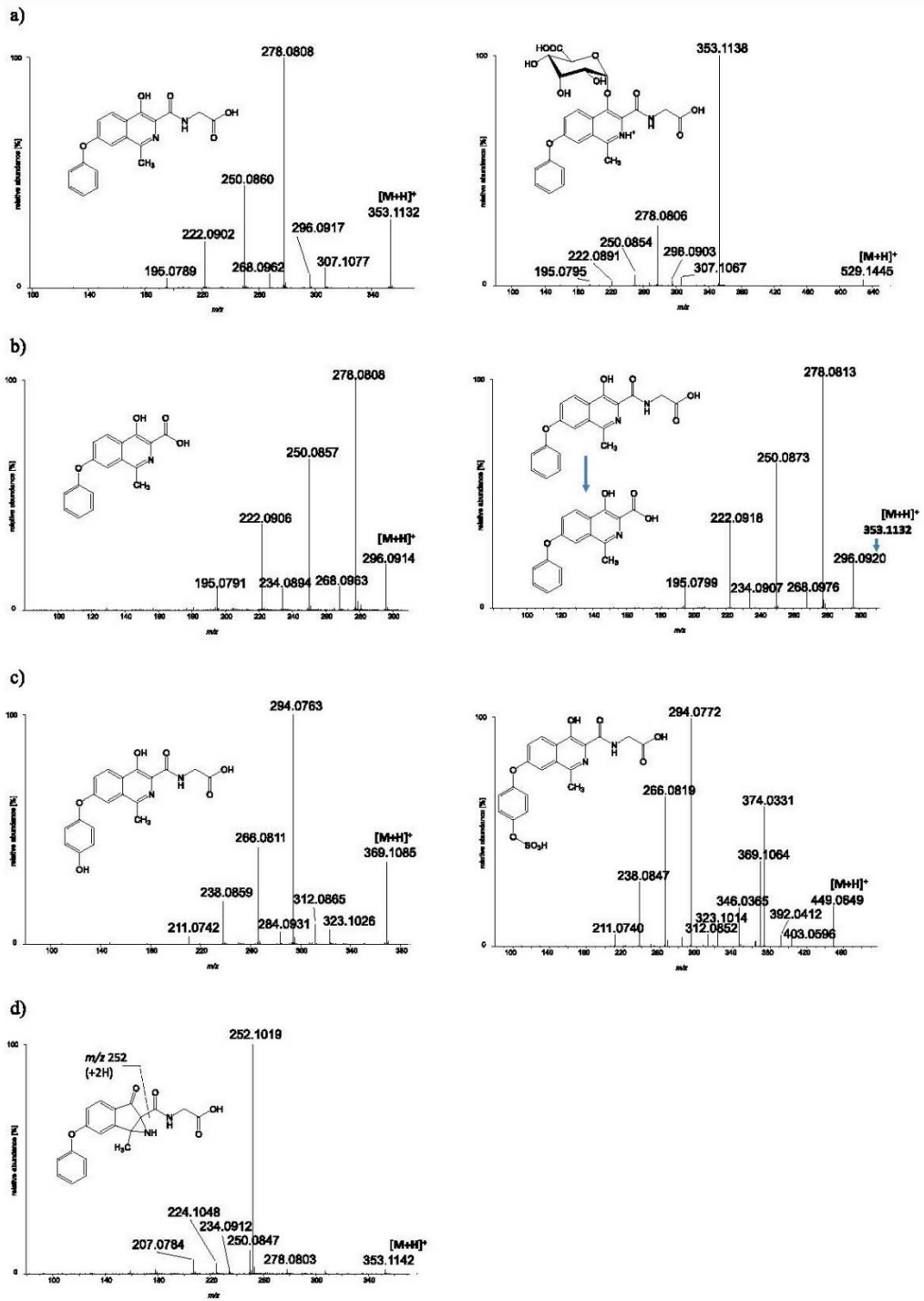
Drug Testing and Analysis

Received: 21 February 2017 Revised: 31 March 2017 Accepted: 31 March 2017 Published online in Wiley Online Library: 31 May 2017

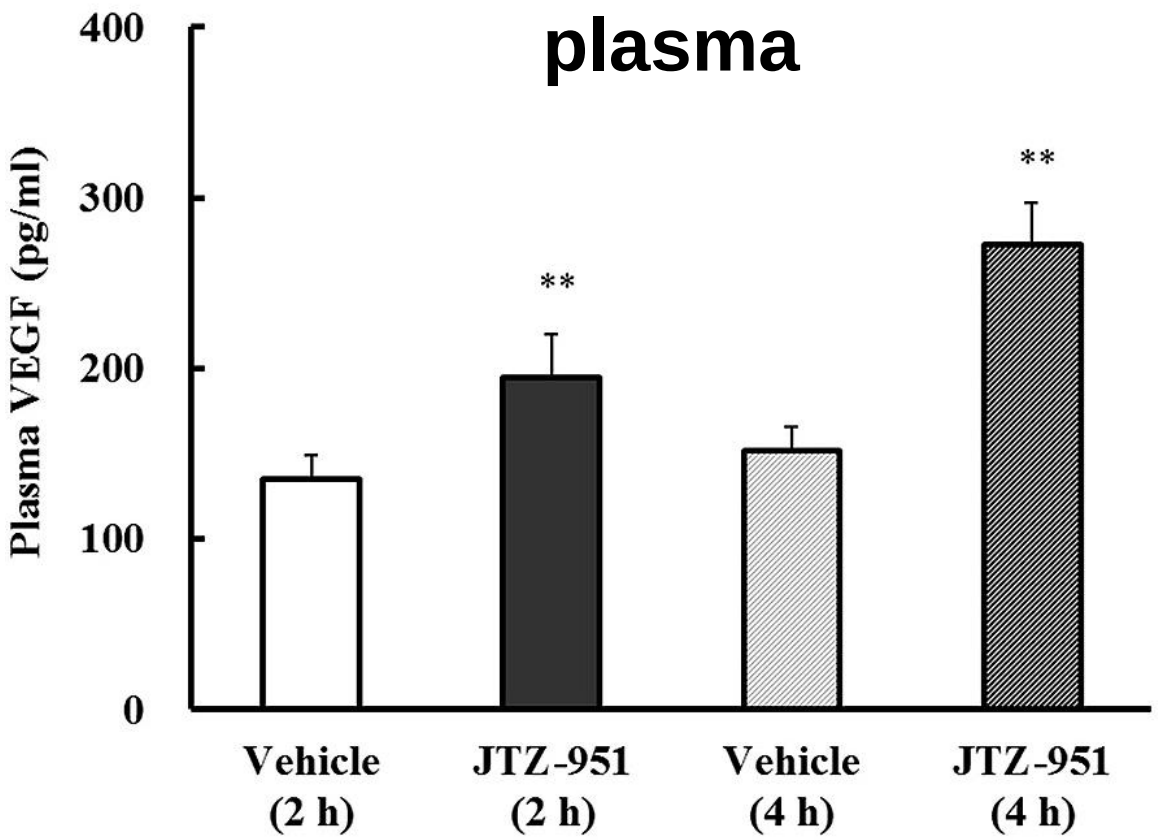
(www.drugtestinganalysis.com) DOI 10.1002/dta.2202

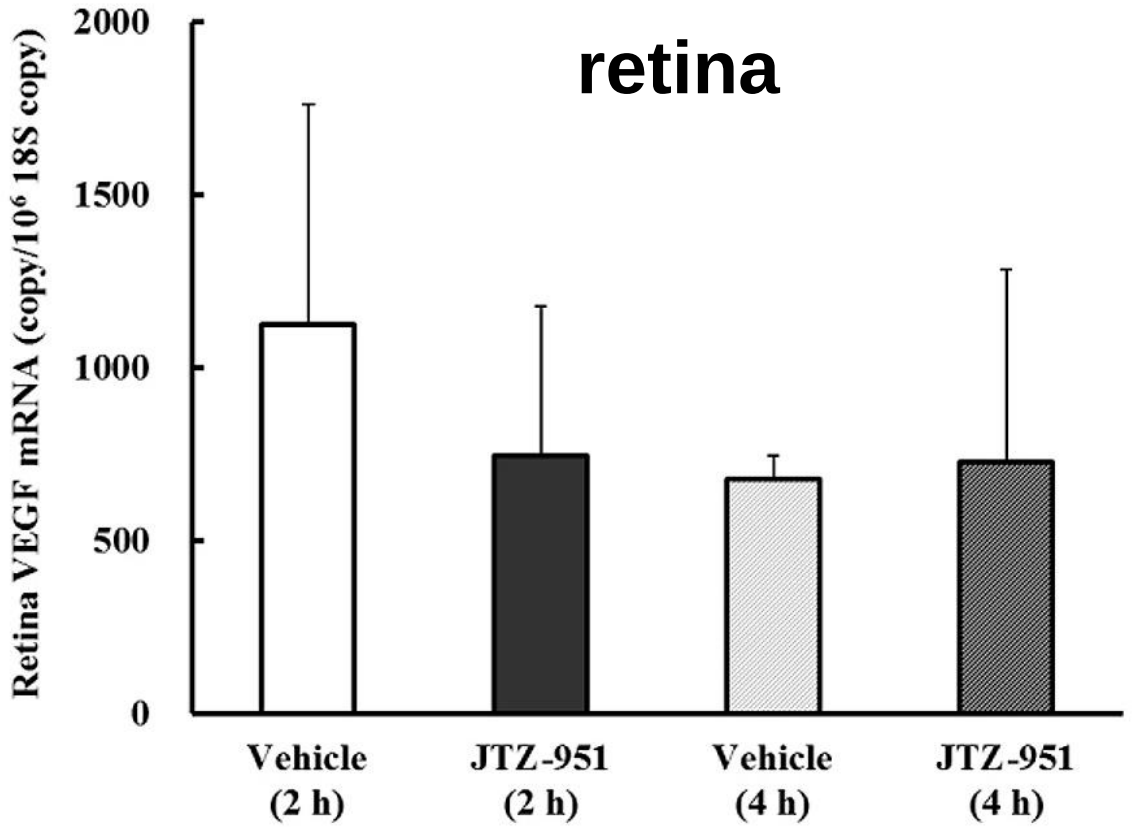
Implementation of the prolyl hydroxylase inhibitor Roxadustat (FG-4592) and its main metabolites into routine doping controls

Daniel Eichner,[a] Ryan M. Van Wagoner,[a] Mitch Brenner,[b] James Chou,[b] Scott Leigh,[b] Lee R. Wright,[b] Lee A. Flippin,[b] Michael Martinelli,[b] Oliver Krug,[c,d] Wilhelm Schänzer[c] and Mario Thevis[c,d]*



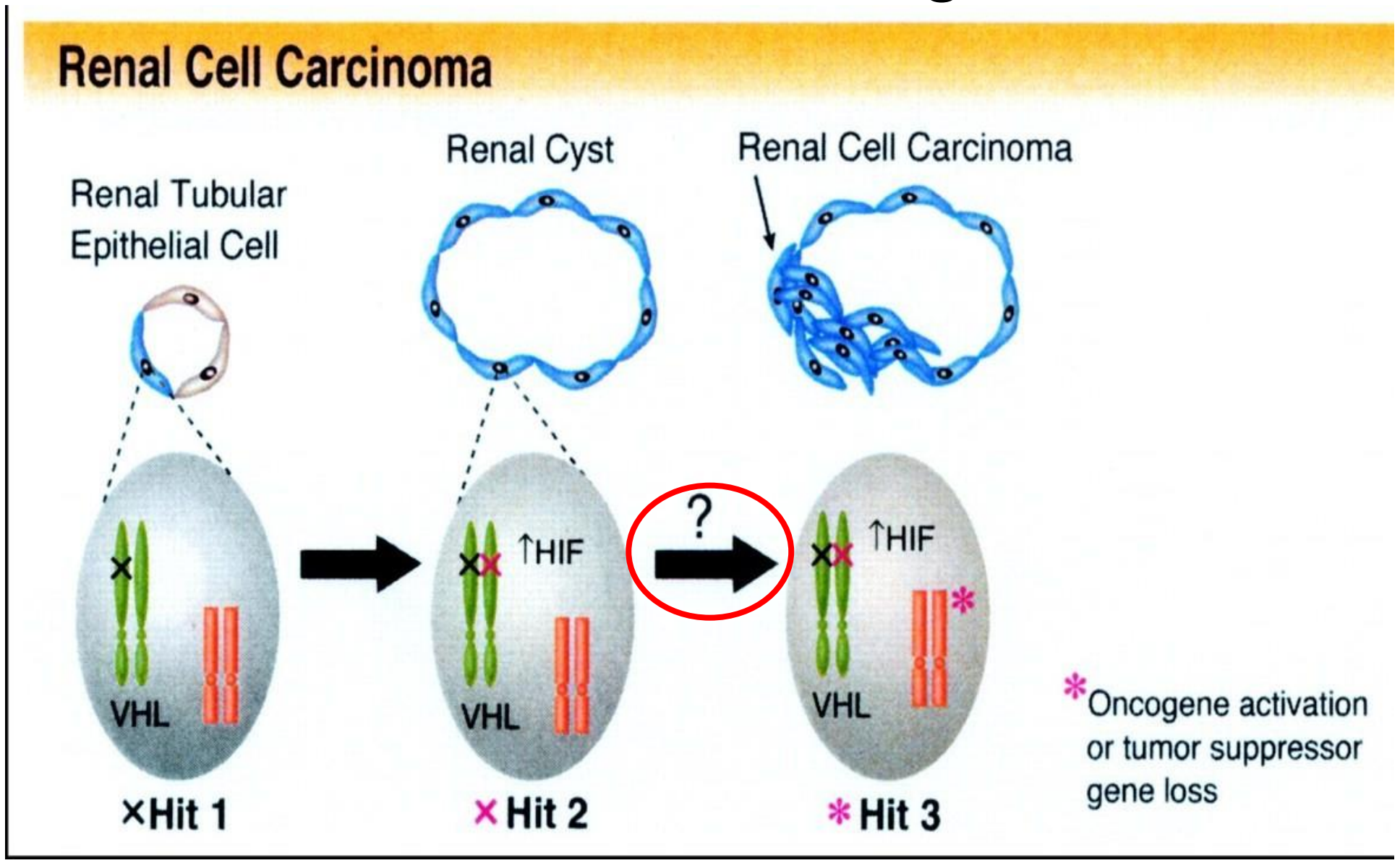
Effects of enarodustat on VEGF production





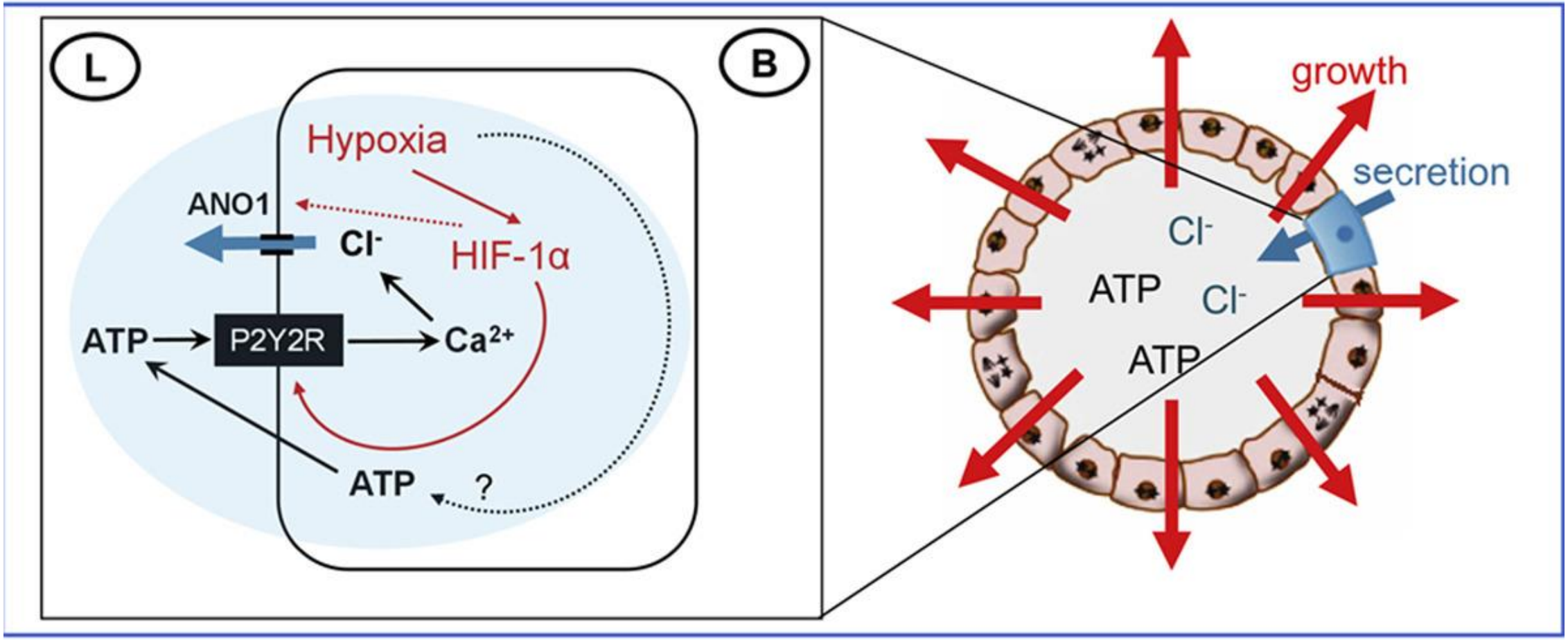
Fukui, Nangaku et al. Eur J Pharmacol 2019

HIF is not an oncogene



Kim & Kaelin. J Clin Oncol 2004

HIF-1α promotes cyst progression in a mouse model of ADPKD



HIF-1α promotes cyst growth in PKD, presumably through calcium-activated chloride secretion

Kraus et al. Kidney Int 2018

hyperkalemia

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat in NDD-CKD patients	Roxadustat (n = 88)	Placebo (n = 28)
Baserab et al. NDT 2015	4 (4.5)	0
Phase 2 studies of roxadustat for treatment of anemia in China (NDD-CKD study)	Roxadustat (n = 61)	Placebo (n = 30)
Chen et al. NDT 2017	6 (10)	2 (7)
DIALOGUE 1	Molidustat (n = 101)	Placebo (n = 20)
Macdougall et al. CJASN 2019	4 (4)	3 (15)
phase 2b multicenter, randomized, double-blind, placebo-controlled in patients with NDD-CKD	Vadadustat (n = 138)	Placebo (n = 72)
Pergola et al. KI 2016	7 (5.1)	0

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