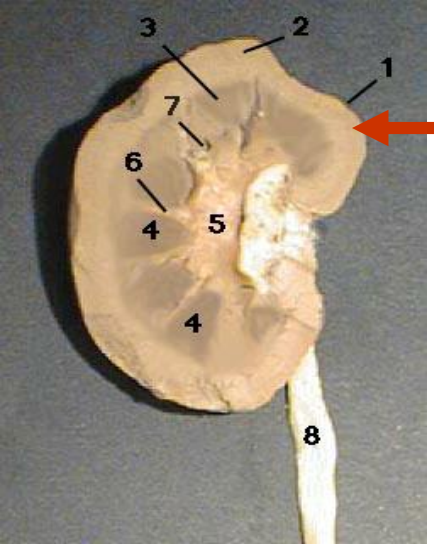
DESC de Réanimation d'île de France 2018

Module Insuffisance Rénale, Nutrition et Métabolisme

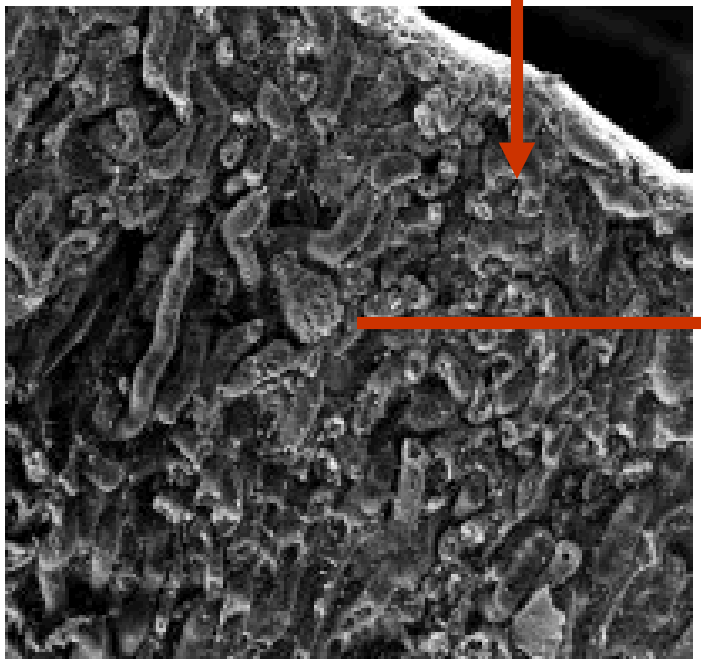
La récupération rénale

Pr. Alexandre HERTIG
Urgences Néphrologiques et Transplantation Rénale, Hôpital Tenon,
Sorbonne Université (Paris 6)

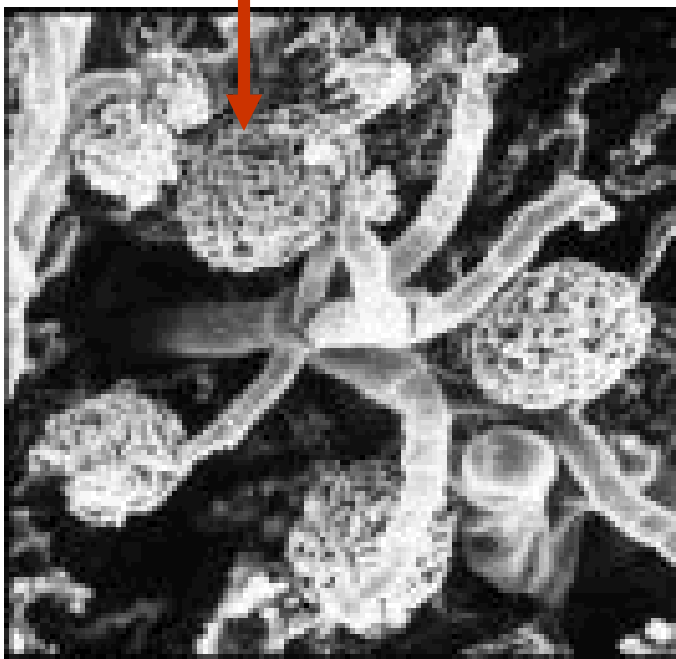
Paris, le 19 mai 2017

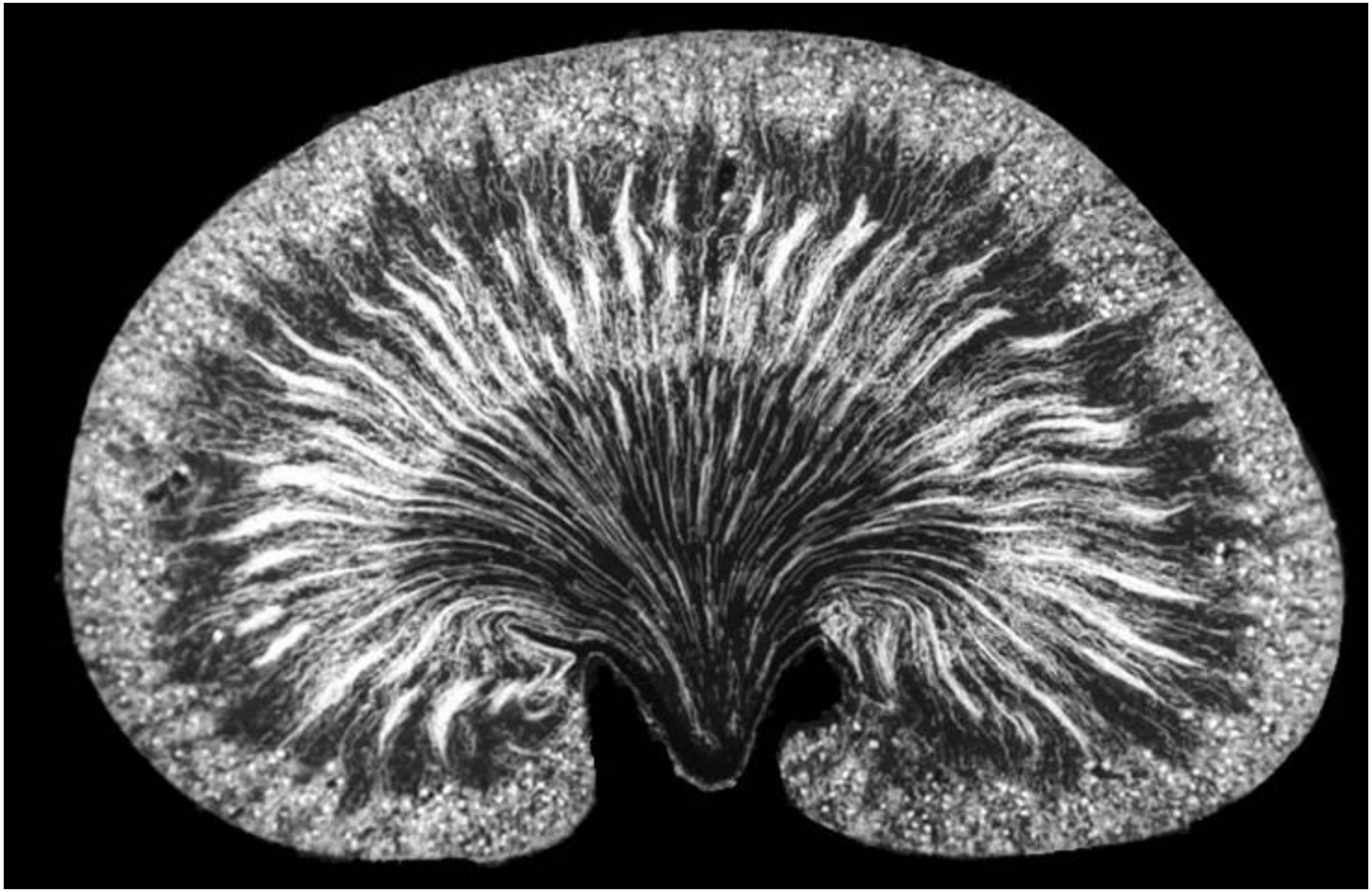


CORTEX

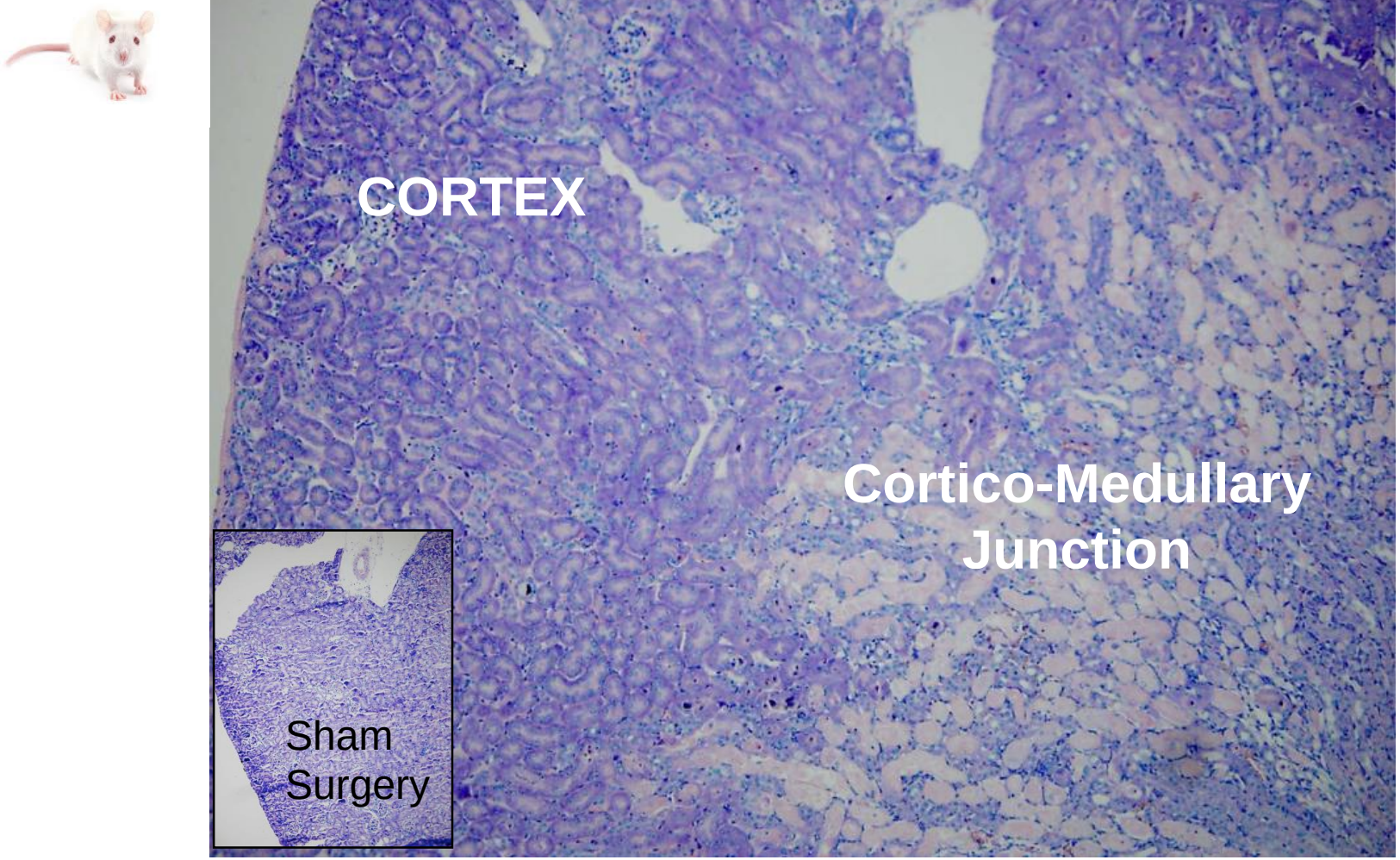


Glomérule

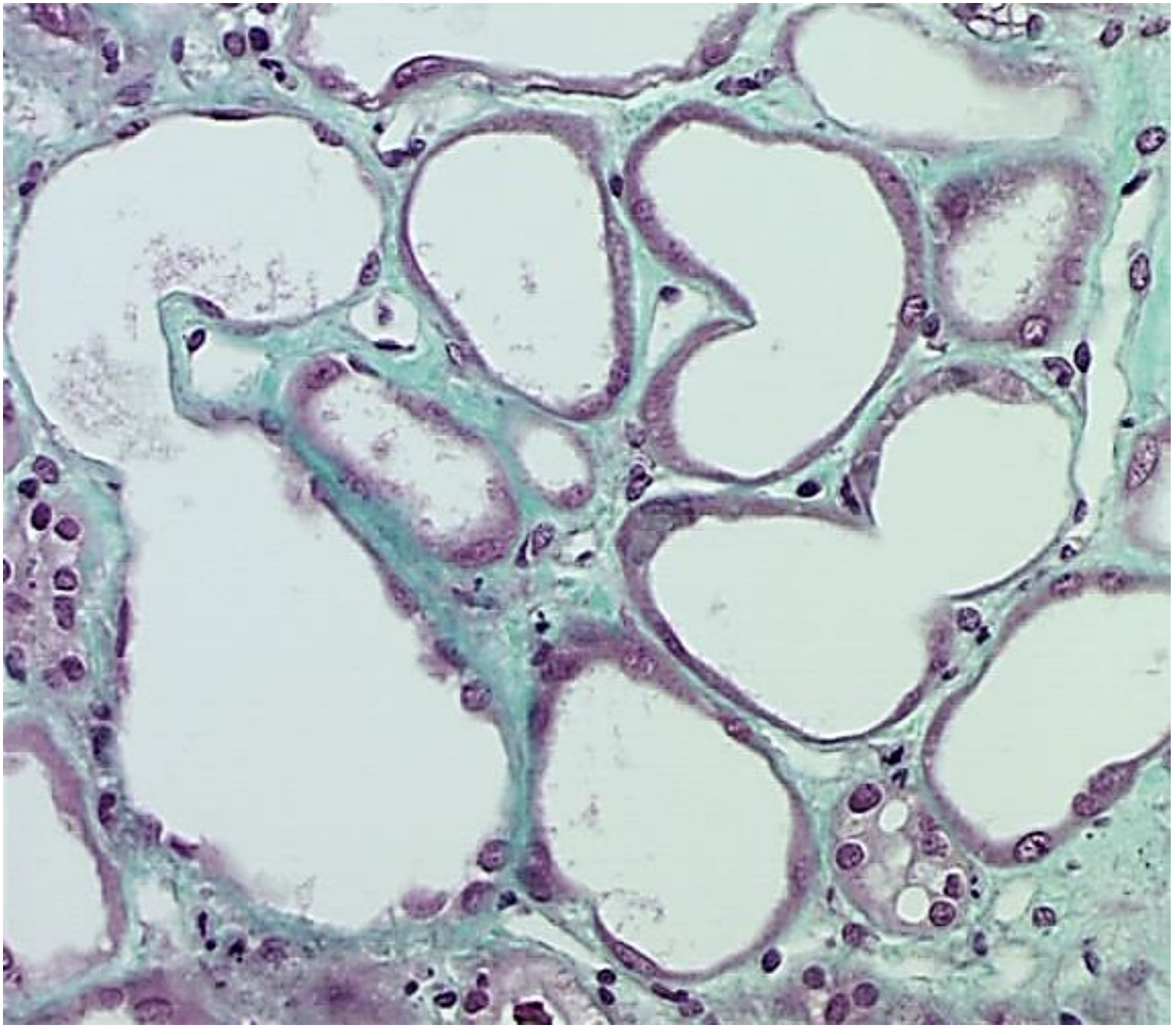




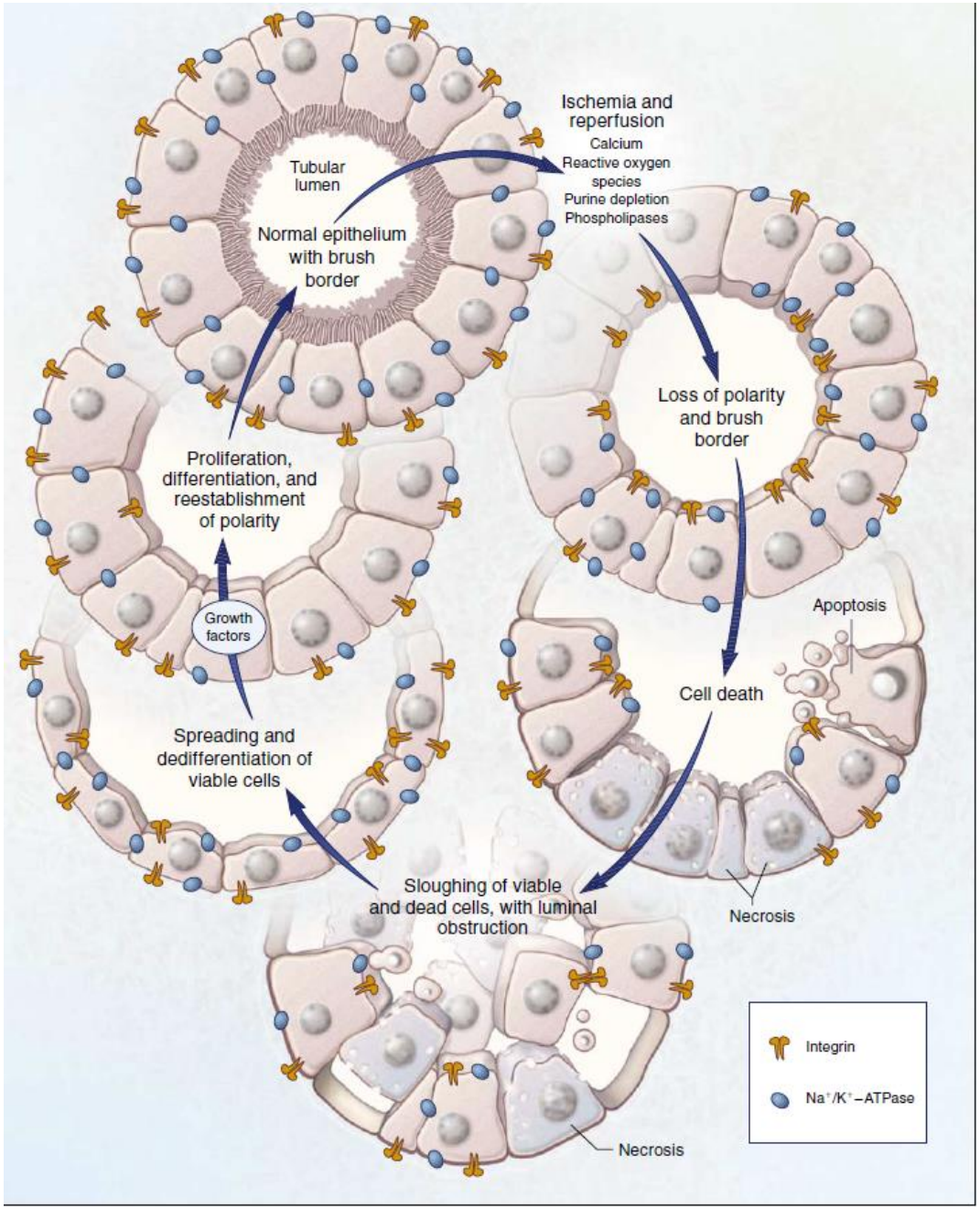
Acute tubular necrosis induced by ischemia reperfusion injury



Giemsa

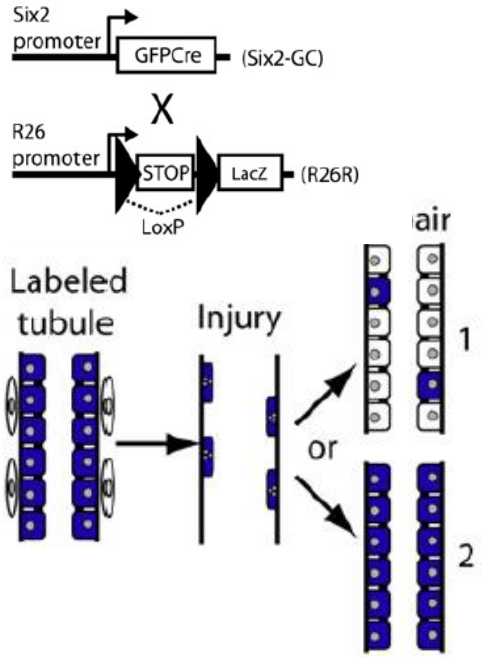


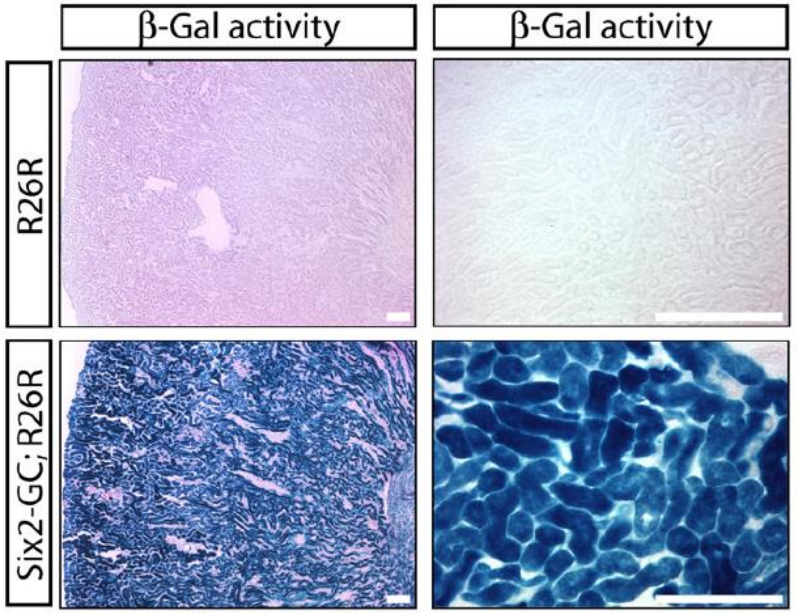
« The severely damaged kidney can completely restore its structure and function »

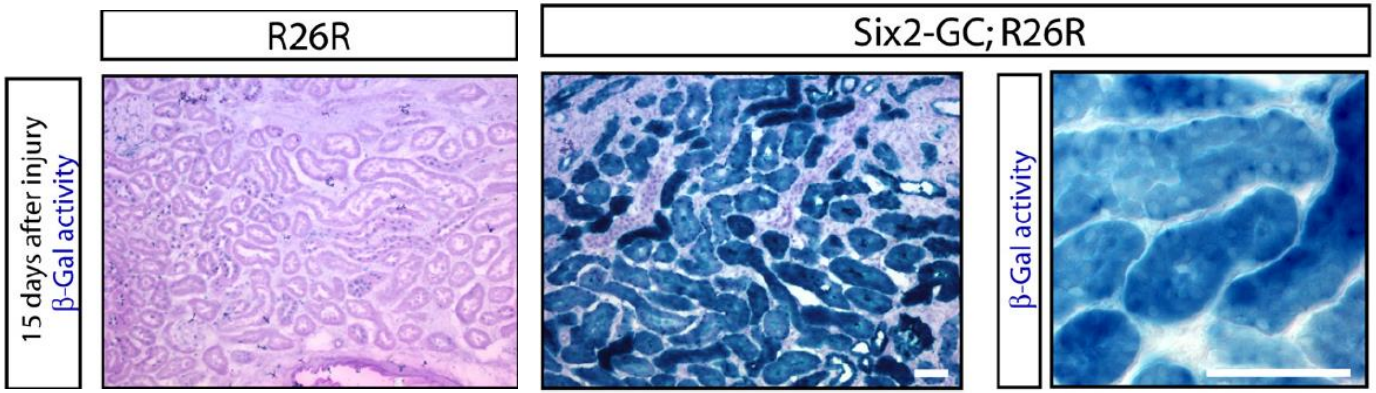


Thadhani R et al, N Engl J Med 1996

C’ est l’ épithélium tubulaire survivant qui répare l’ épithélium nécrosé

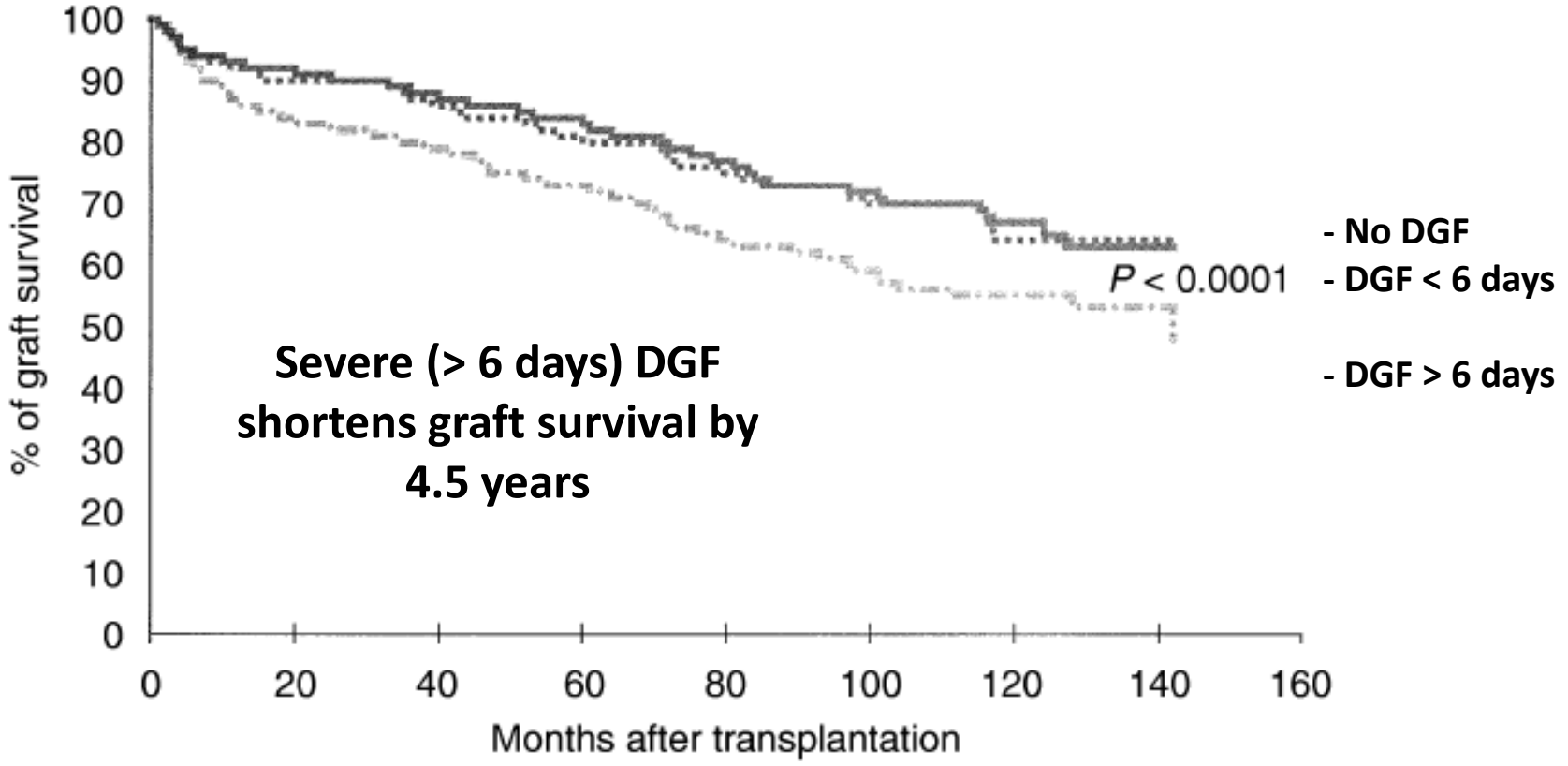






Humphreys BD, Cell Stem Cell 2008

IMPACT OF DELAYED GRAFT FUNCTION



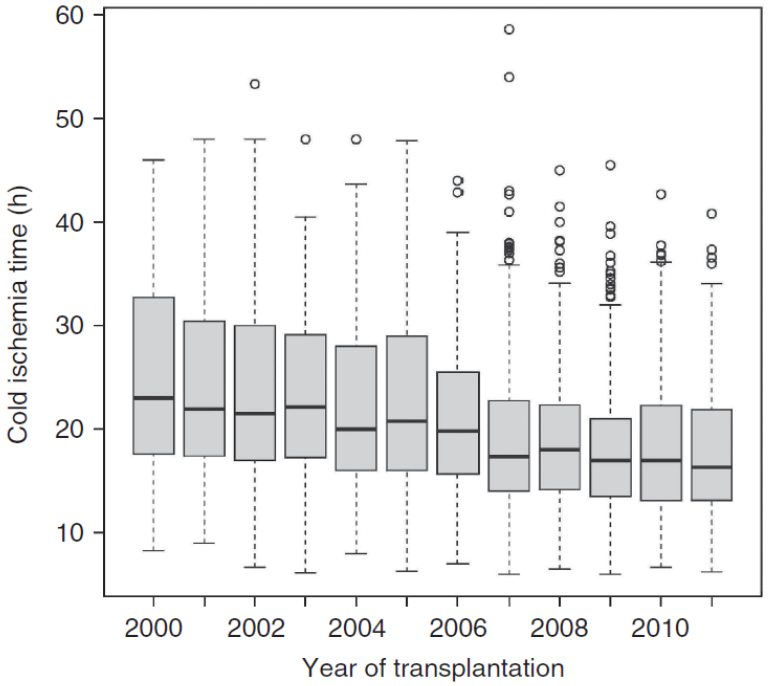
Giral M et al, Kidney Int 1998

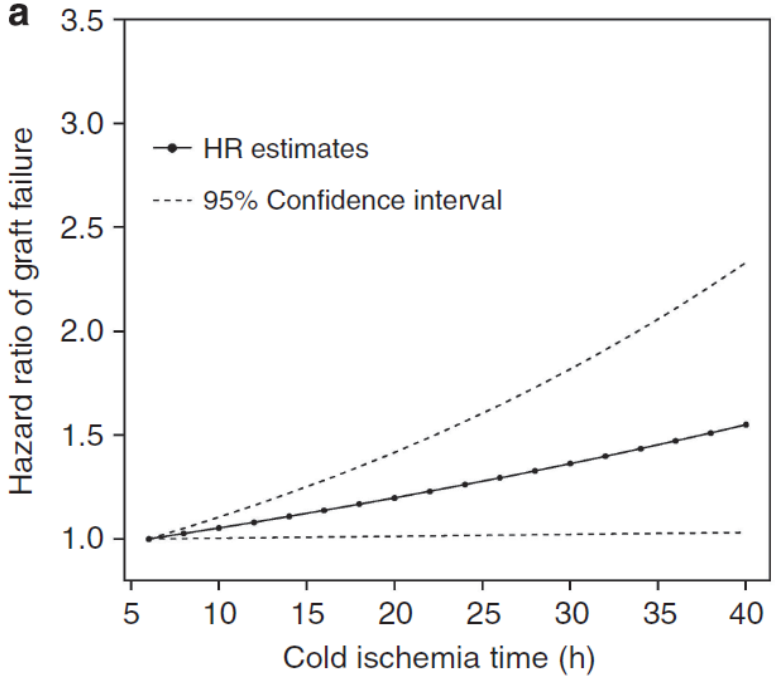
USRDS DATA (2013): Odds Ratio for graft loss at 5 years: 1.7 (after exclusion of ECD)

Butala et al, Transplantation 2013

Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation

Agnes Debout[1,11], Yohann Foucher[1,2,11], Katy Trébern-Launay[1,2], Christophe Legendre[3,4], Henri Kreis[3,4], Georges Mourad[5], Valérie Garrigue[5], Emmanuel Morelon[6], Fanny Buron[6], Lionel Rostaing[7,8], Nassim Kamar[7,8], Michèle Kessler[9], Marc Ladrière[9], Alexandra Poignas[10], Amina Blidi[2], Jean-Paul Soulillou[1], Magali Giral[1,10,11] and Etienne Dantan[2,11]





Kidney International, 2014

CLINICAL RESEARCH www.jasn.org

Acute Kidney Injury Increases Risk of ESRD among Elderly

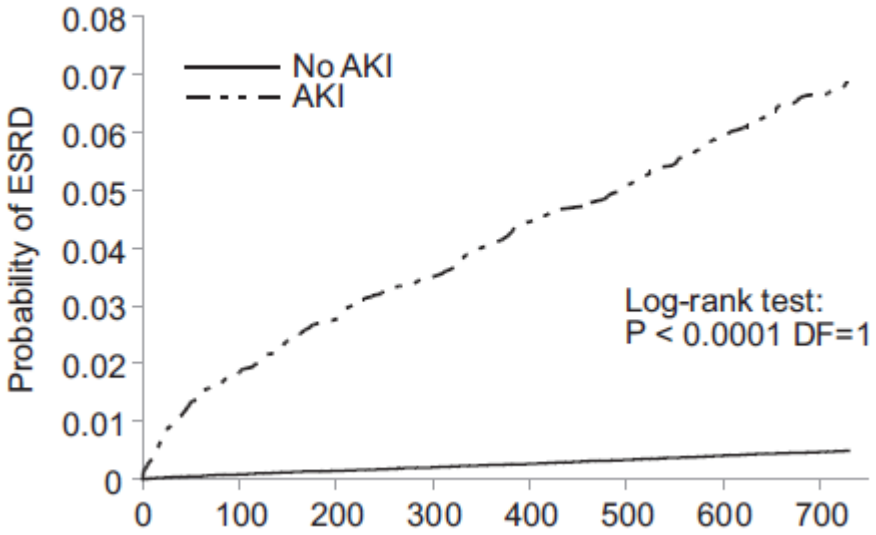
Areef Ishani,* Jay L. Xue,* Jonathan Himmelfarb,† Paul W. Eggers,‡ Paul L. Kimmel,‡§
Bruce A. Molitoris,‖ and Allan J. Collins*

Medicare (US), année 2000

233 803 patients > 67 ans

3,1% AKI
HR for ESRD: **13 if CKD-free**
41 if CKD
(8 if CKD no AKI)

5,3‰ ESRD: 25% ATCD d'AKI



Ishani A, J Am Soc Nephrol 2009 (January)

Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease

Lowell J. Lo[1], Alan S. Go[1,2,3], Glenn M. Chertow[4], Charles E. McCulloch[3], Dongjie Fan[2], Juan D. Ordoñez[5] and Chi-yuan Hsu[1,2]

Caifornie, 1996-2003

562 799 H
(GFR pre H > 45 mL/min)

703 AKI HD
295 morts
65 HDC
343 vivants et sortis de HD

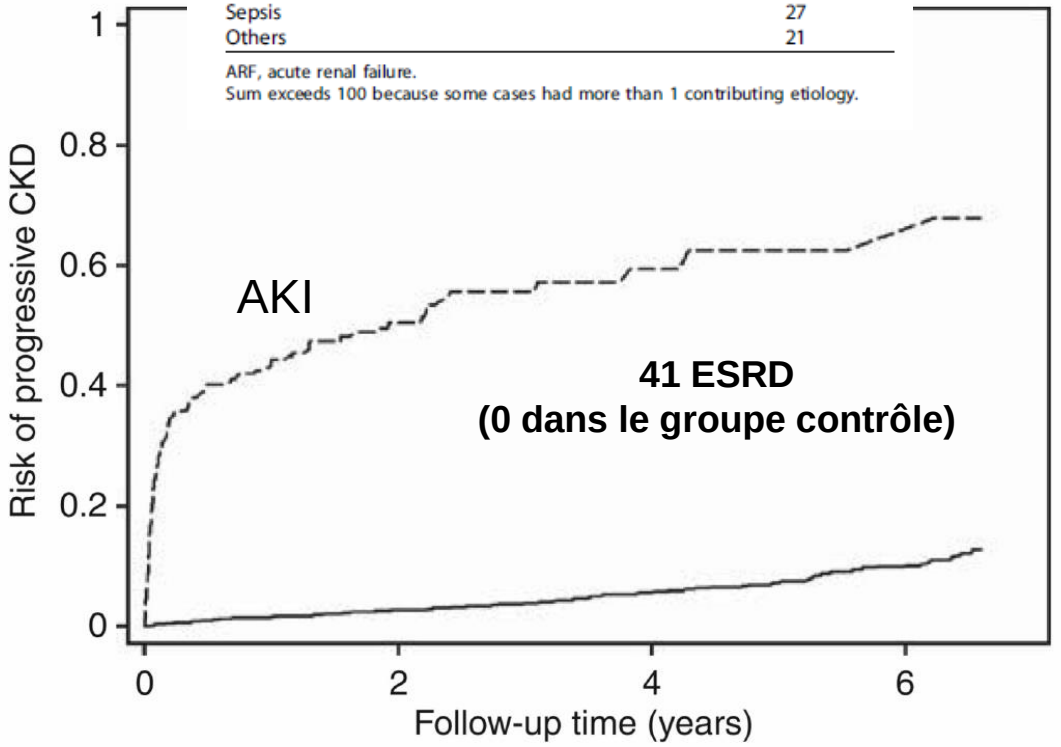
HR CKD: x 28.1*

(*) variables d'ajustement:
Âge, sex, black, diabetes, HTA, protéinurie, eGFR < 45 ml/min avant l'admission

Table 2 | Diagnoses given for ARF by random chart review (*N* = 100)

Diagnosis	
Decreased renal perfusion (including volume contraction, congestive heart failure, hypotension, and cardiac arrest)	49
Medication-related	22
Radiocontrast media	7
Post-operative	13
Sepsis	27
Others	21

ARF, acute renal failure.
Sum exceeds 100 because some cases had more than 1 contributing etiology.



Lo LJ, Kidney Int 2009 (June)

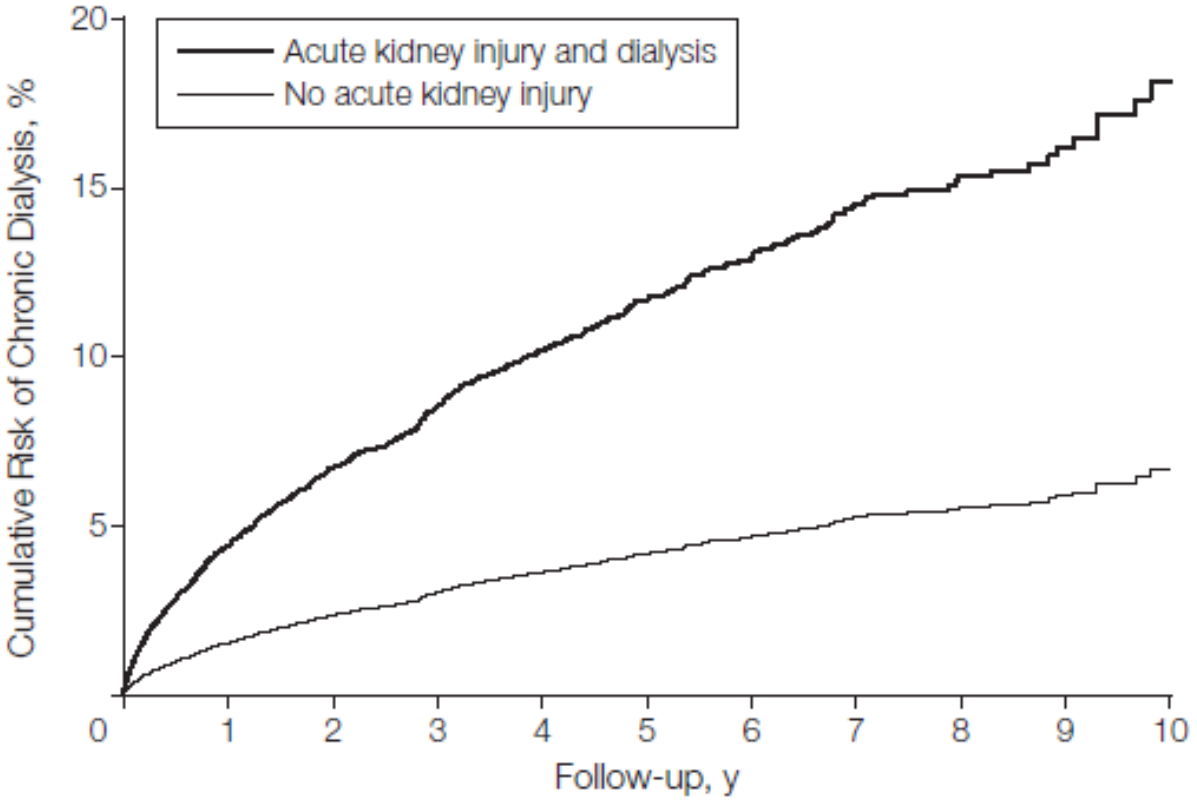
Chronic Dialysis and Death Among Survivors of Acute Kidney Injury Requiring Dialysis

1996-2006
All Ontario

3769 AKI HD
X4: 13598 contrôles*****

Suivi médian 3 ans
Incidence ESRD
2.63%/an vs 0.91
HR ESRD: x 3.23

(*****) appariés sur âge, sexe, VM, score de propensité à AKI – 25% CKD



Procedure or condition during index hospitalization	With Acute Kidney Injury and Dialysis at Index Hospitalization (n = 3769)[a]	Without Acute Kidney Injury or Dialysis at Index Hospitalization (n = 13 598)[a]
Mechanical ventilation	1761 (46.7)	5700 (41.9)
Sepsis	579 (15.4)	2045 (15.0)
Cardiac surgery	435 (11.5)	1365 (10.0)
Noncardiac arterial angiography	312 (8.3)	1210 (8.9)
Coronary angiography with or without percutaneous coronary intervention	289 (7.7)	1153 (8.5)
Abdominal aortic aneurysm repair	153 (4.1)	458 (3.4)

Wald R, JAMA, September 2009

Increased risk of death and *de novo* chronic kidney disease following reversible acute kidney injury

Ion D. Bucaloiu[1], H. Lester Kirchner[2], Evan R. Norfolk[1], James E. Hartle II[1] and Robert M. Perkins[1,3]

[1]Department of Nephrology, Geisinger Medical Center, Danville, Pennsylvania, USA; [2]Biostatistics and Research Data Core, Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA and [3]Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA

30 207 patients

Suivis 3 ans en moyenne

1610 reversible AKI

Hazard Ratio of *de novo* CKD 1,9

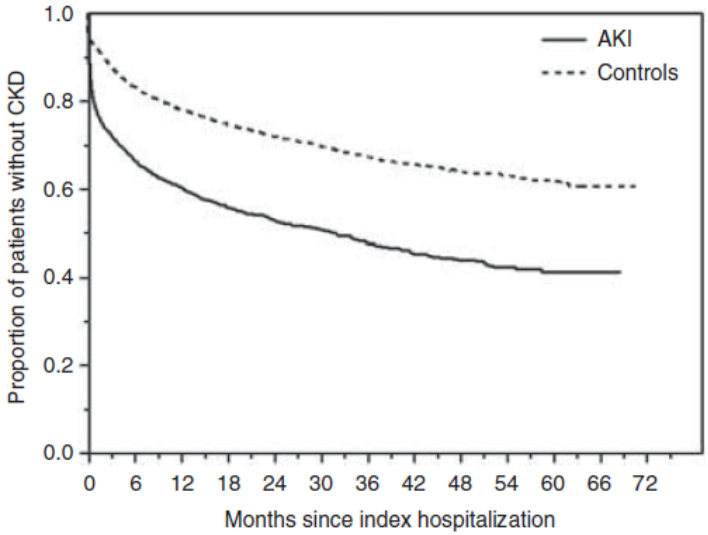


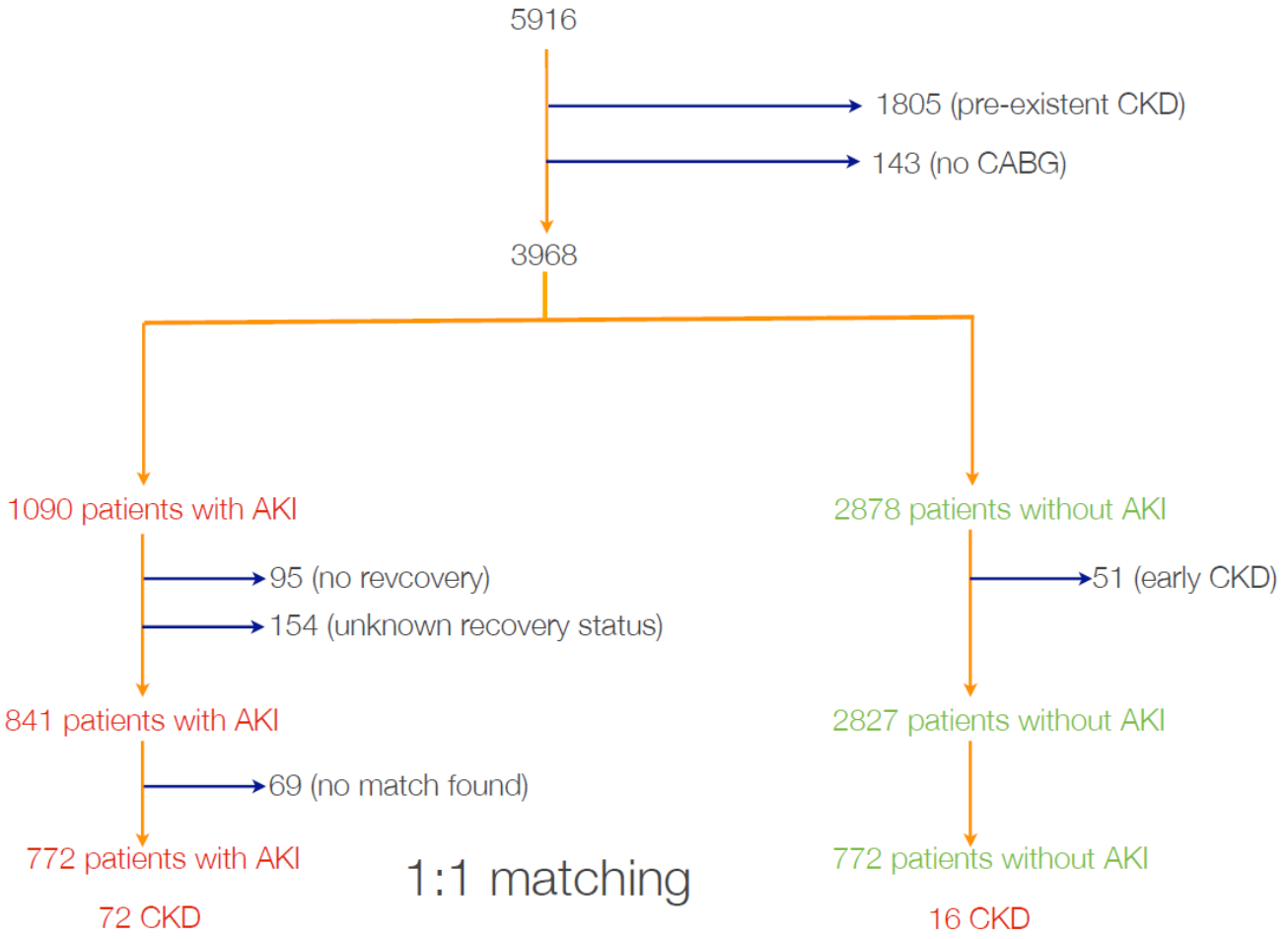
Figure 2 | Cumulative incidence of chronic kidney disease (CKD) by exposure status (recovered acute kidney injury (AKI) group vs. controls) among patients with normal baseline kidney function.

Bucaloiu ID, Kidney Int 2012

Etude en chirurgie cardiaque

Caen et Bichat, 2005-2013

David Legouis



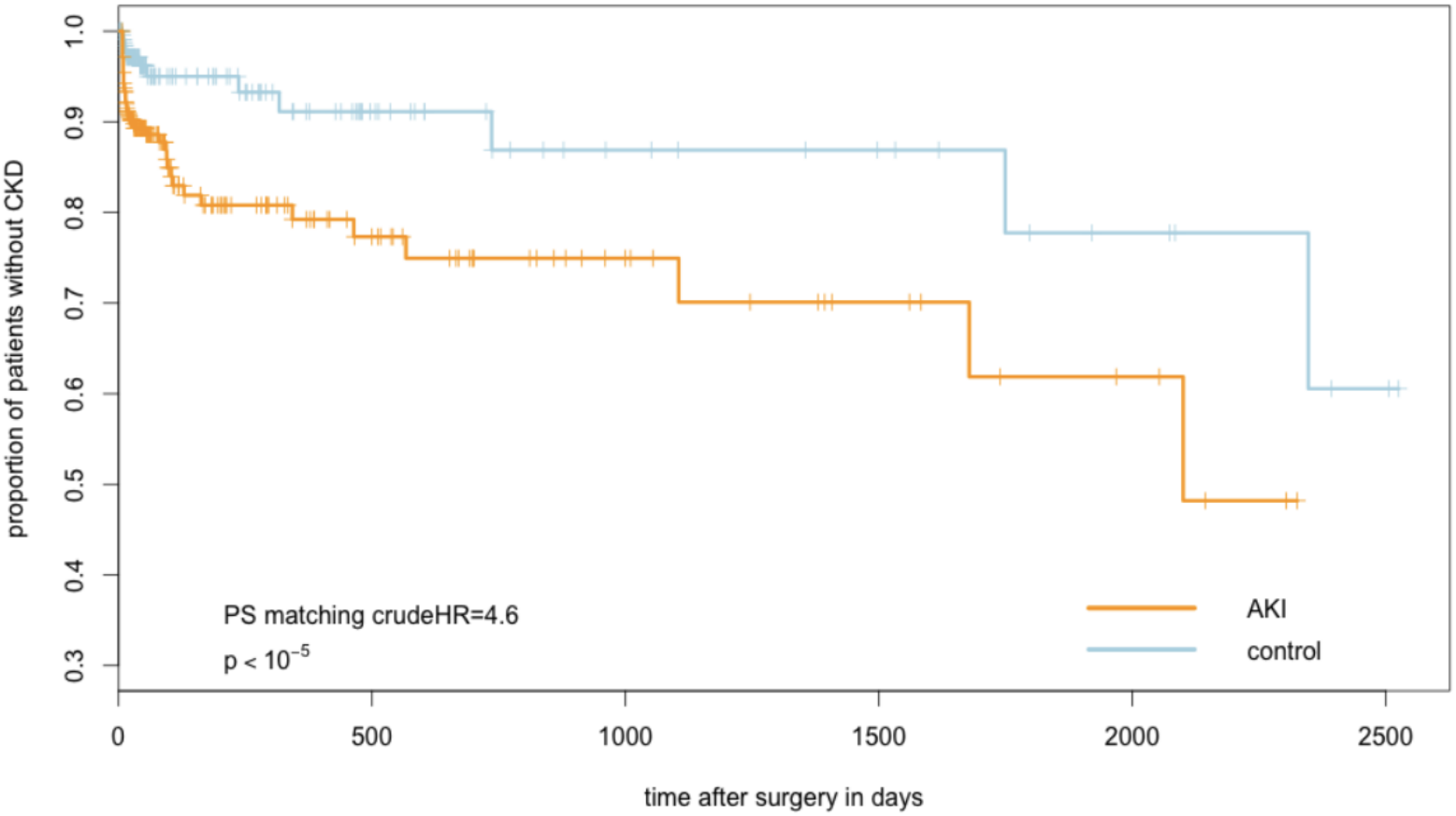
Legouis D et al, Anesthesiology 2017

Appariement sur le score de propensité à développer une AKI

	AKI	CTRL	Absolute SD
Propensity score - mean(SD)	0.28	0.28	0.15
Baseline eGFR (mL/min/1.73m^2)-mean(SD)	78	77	6.7
Age (years) - mean(SD)	66	67	5.5
Euroscore (%) - mean(SD)	4.3	4.3	0.18
BMI - mean(SD)	27	27	5.1
Cardiopulmonary bypass time (min) - mean(SD)	83	81	3.5
Clamping time (min) - mean(SD)	61	61	1.2
Male - nb(%)	75	77	4.5
LVEF (%) - mean(SD)	56	56	0.6
Smoker - nb(%)	17	17	1.0
Mellitus diabetes - nb(%)	26	25	2.1

Legouis D et al, Anesthesiology 2017

L'AKI est un facteur de risque de CKD rapide



	Nb of events (%)	Incidence rate (per 100 person-Years)
With AKI (n=772)	72 (9.3)	38.4
Without AKI (n=772)	16 (2.1)	10.2

IRR p<10^-8
HR = 4.6 [3.1 ; 7.8]
P<10^-5

Legouis D et al, Anesthesiology 2017

Le pronostic
de la nécrose tubulaire aiguë
n'est pas
systématiquement favorable

même chez ceux qui récupèrent

The NEW ENGLAND JOURNAL of MEDICINE

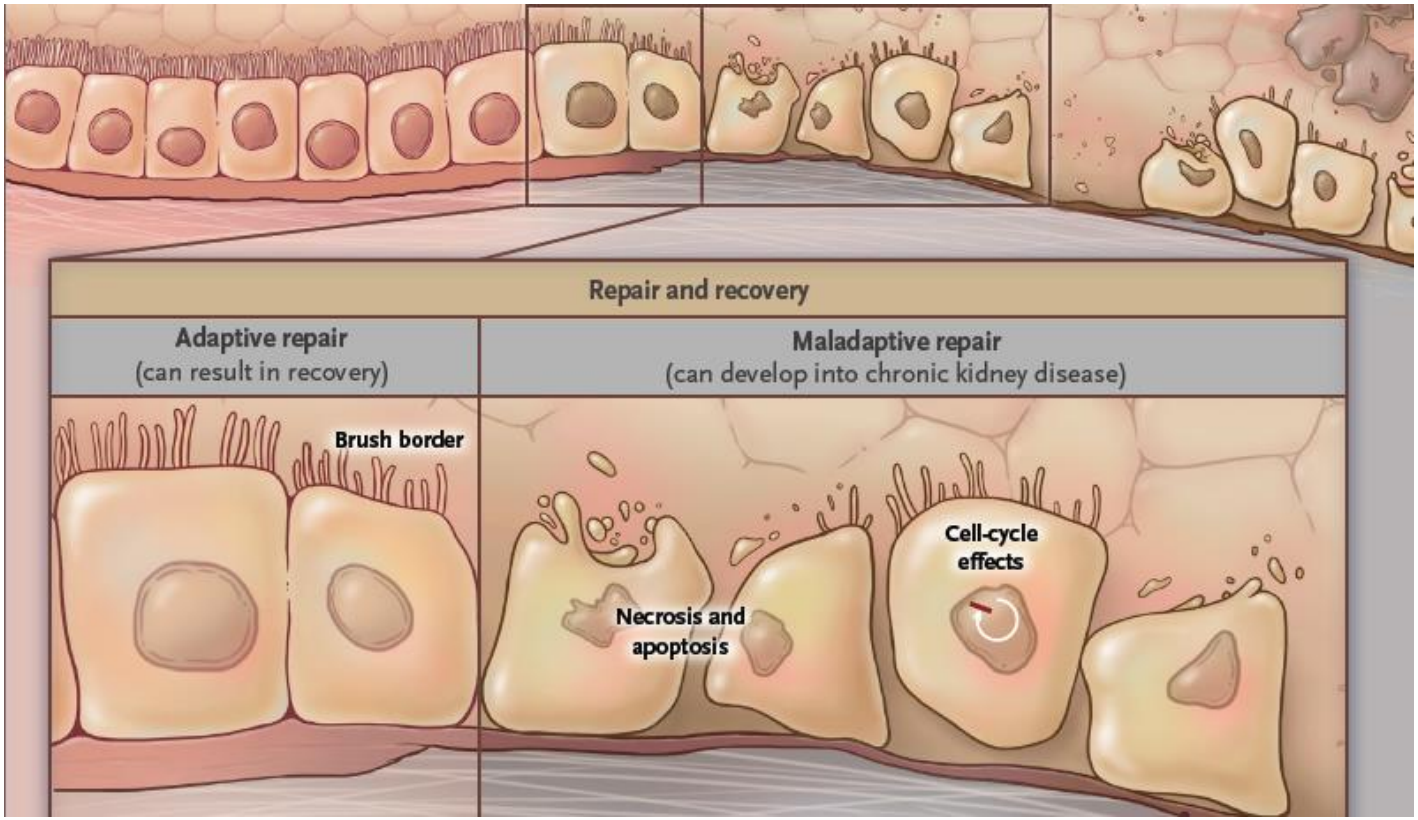
REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes

Lakhmir S. Chawla, M.D., Paul W. Eggers, Ph.D., Robert A. Star, M.D., and Paul L. Kimmel, M.D.

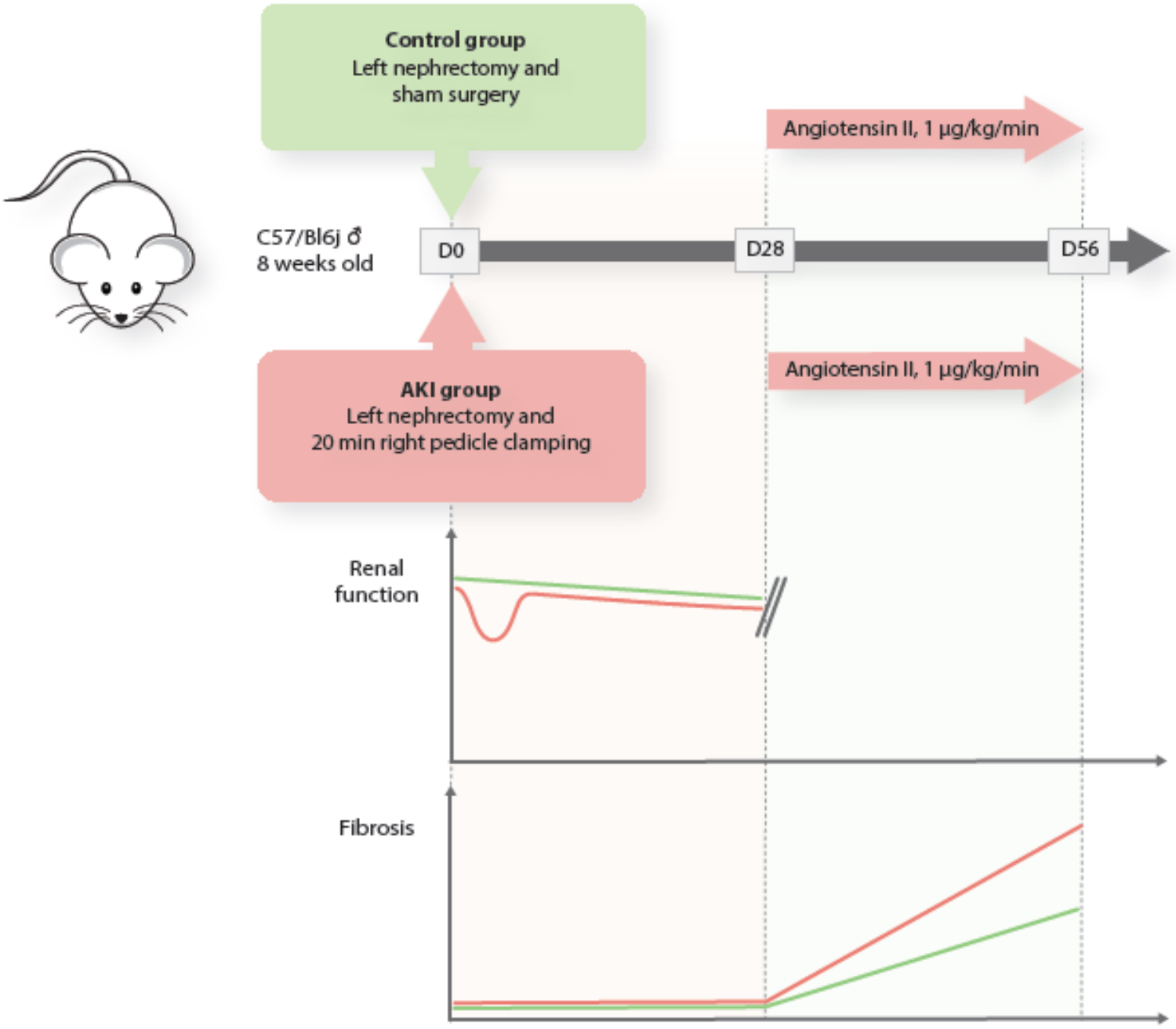
Schématisation de la réparation, *ad integrum*…ou pas

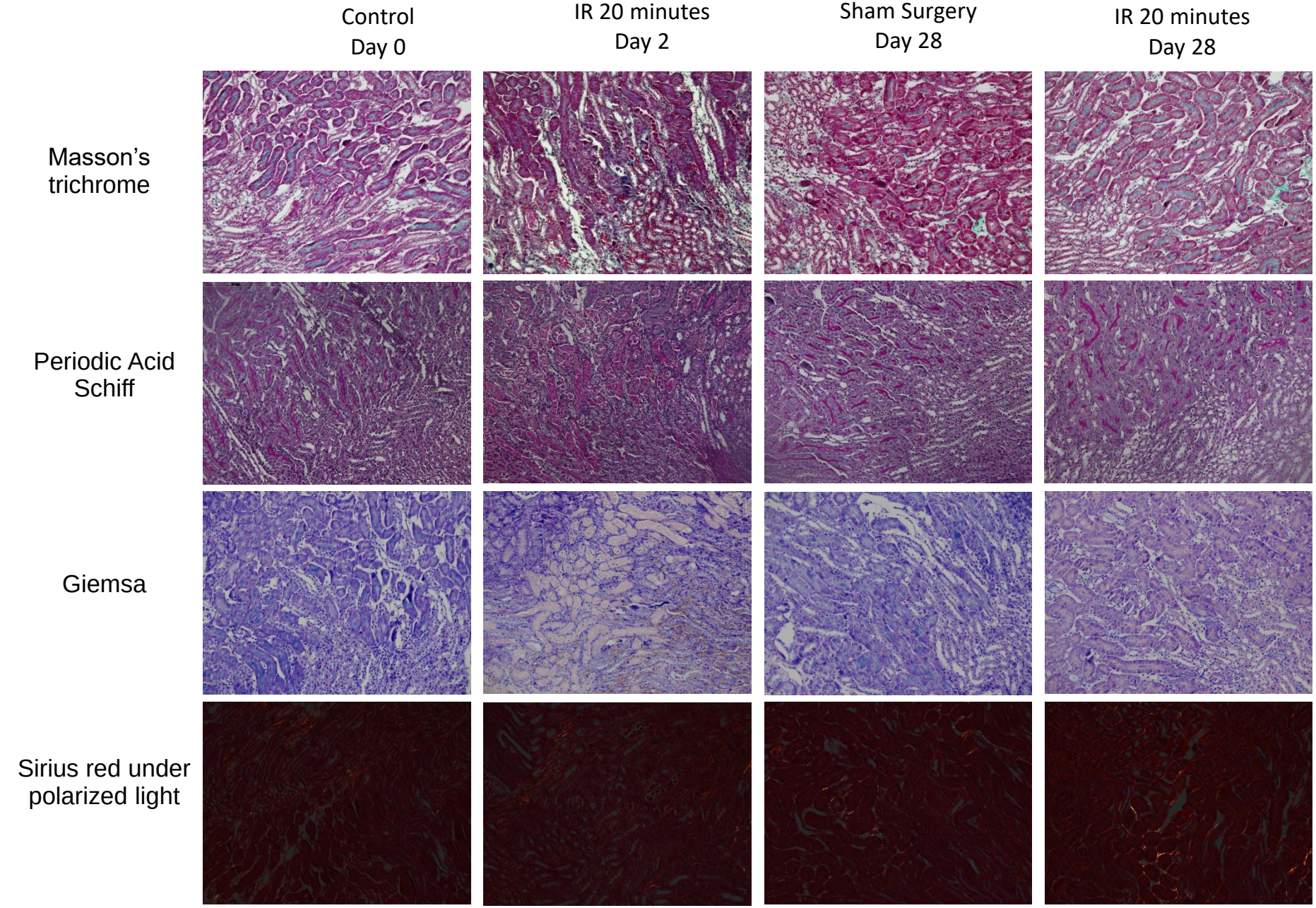


Chawla LS, N Engl J Med 2014

Tout les patients ne développent pas une CKD post-AKI

Faut-il un deuxième hit ?

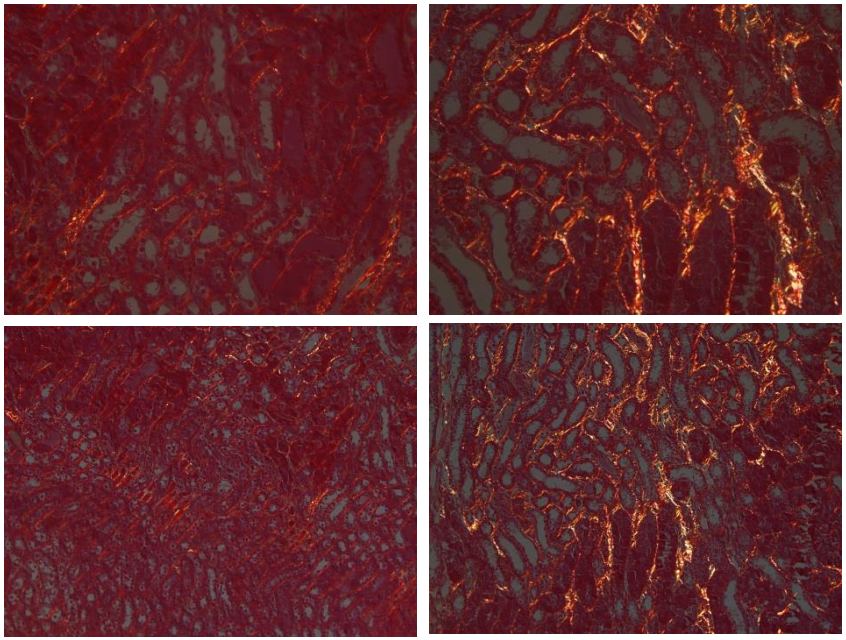

Control group
Left nephrectomy and
sham surgery
Angiotensin II, 1 µg/kg/min
C57/Bl6j ♂
8 weeks old
D0
D28
D56
AKI group
Left nephrectomy and
20 min right pedicle clamping
Angiotensin II, 1 µg/kg/min
Renal
function
Fibrosis


Control
Day 0
IR 20 minutes
Day 2
Sham Surgery
Day 28
IR 20 minutes
Day 28
Masson's trichrome
Periodic Acid Schiff
Giemsa
Sirius red under polarized light

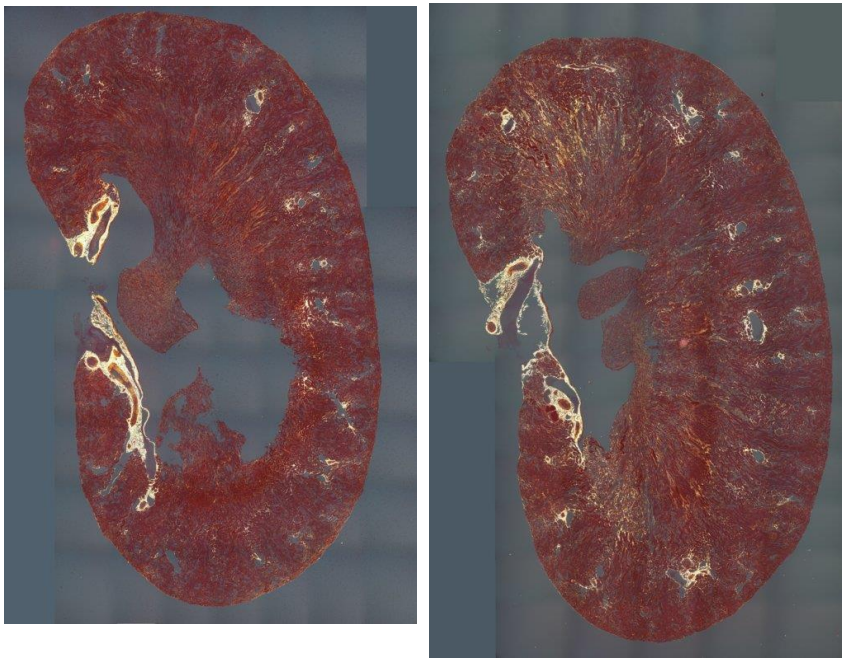
Sham–angio2

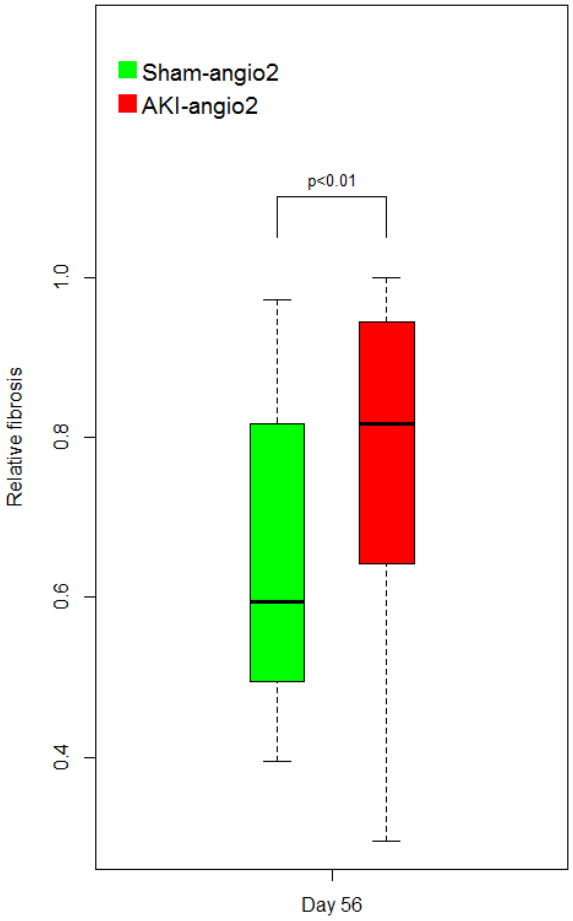
AKI-angio 2

Sirius red under polarized light



Sirius red under polarized light (Image obtained with a full scan of the section)

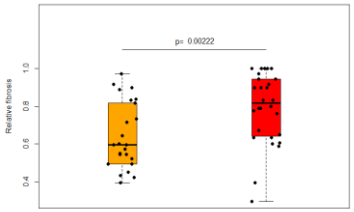




Impact of a resolved AKI on fibrogenesis in the presence of a 2nd hit ?

Fibrotic effect of Angiotensin 2

Morphological comparaison of fibrosis, blindly assessed by two operators

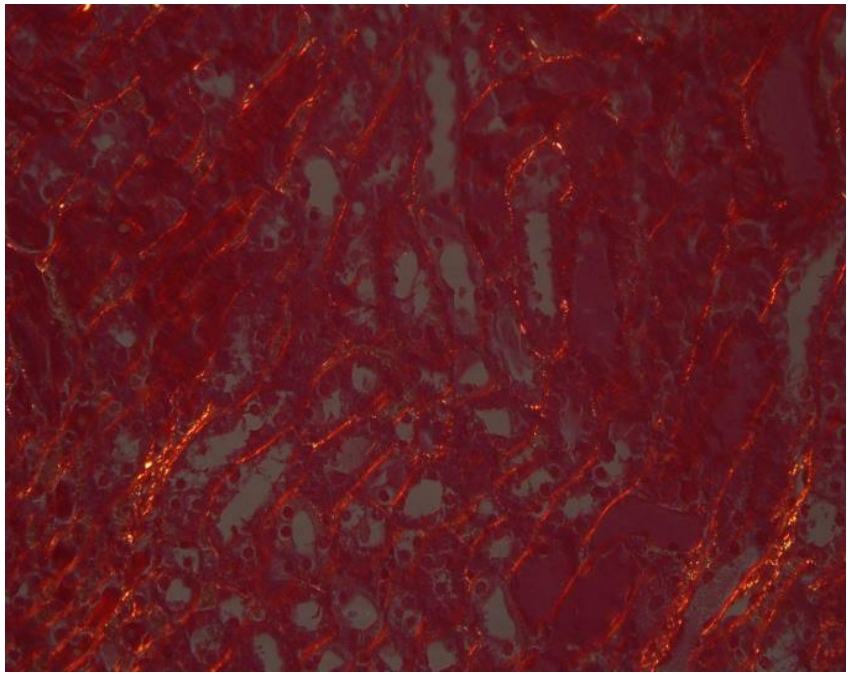


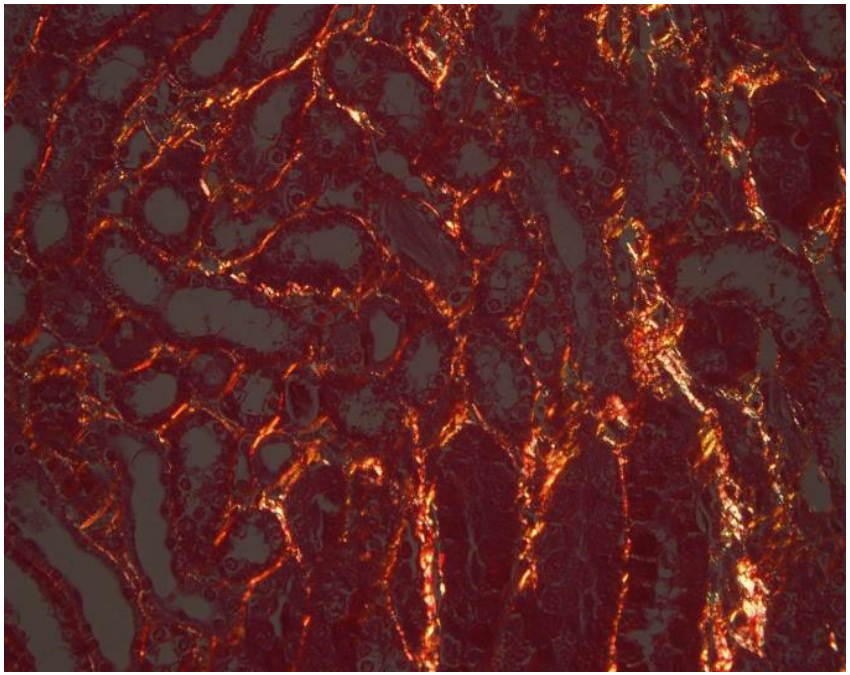
Sham Surgery – angio 2 Day 56

IR 20 minutes – angio 2 Day 56

alone

history of resolving AKI



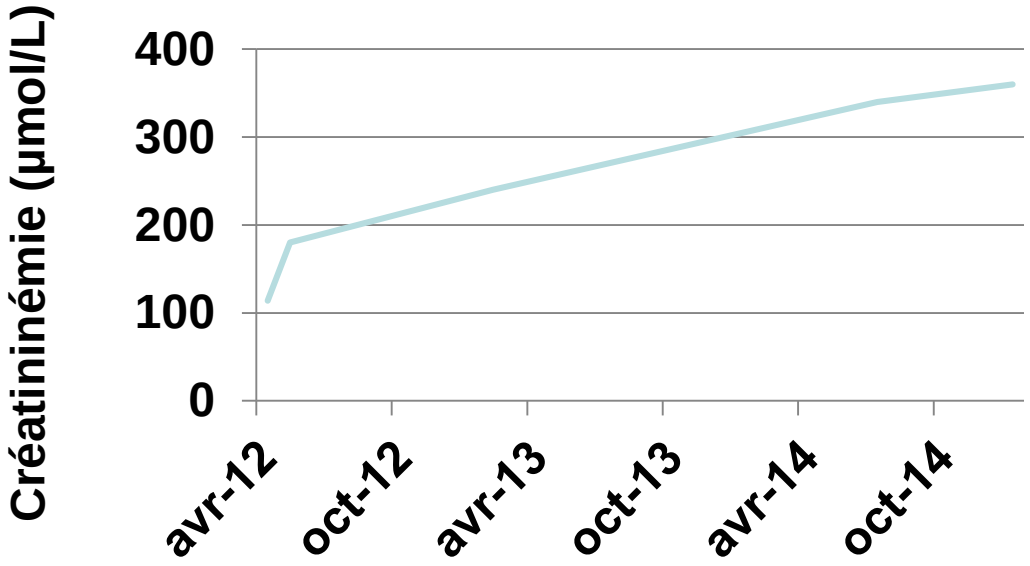


Mr Pascal S. né en 1955 (67 ans)

Employé des pompes funèbres, tabagisme modéré, **éthylisme**

2011: **état de choc** cardiogénique sur cardiopathie dilatée à coronaires saines
IRA / AKI (NTA), récupération complète

Avril 2012: transplantation cardiaque



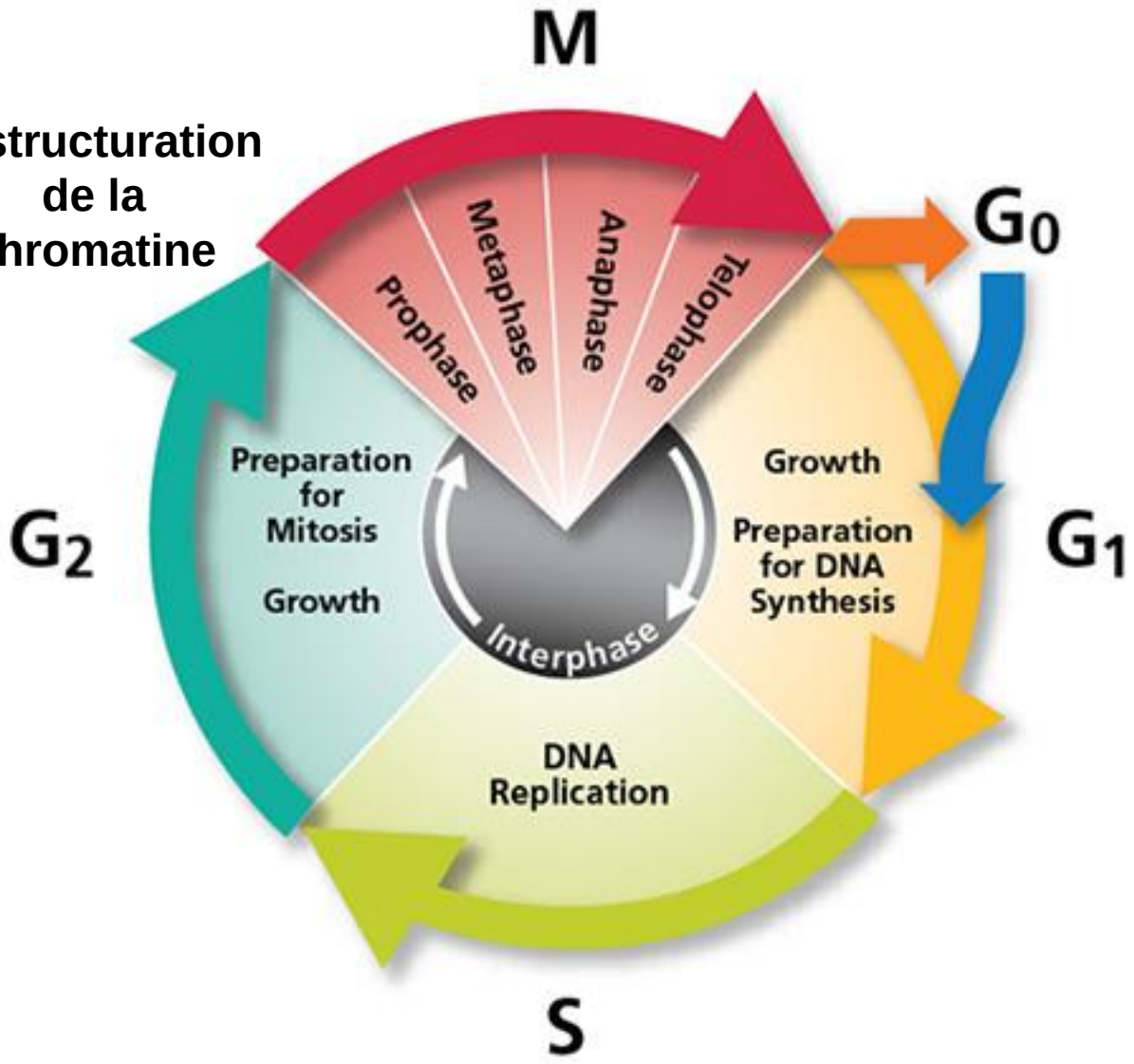
Echographie RAS

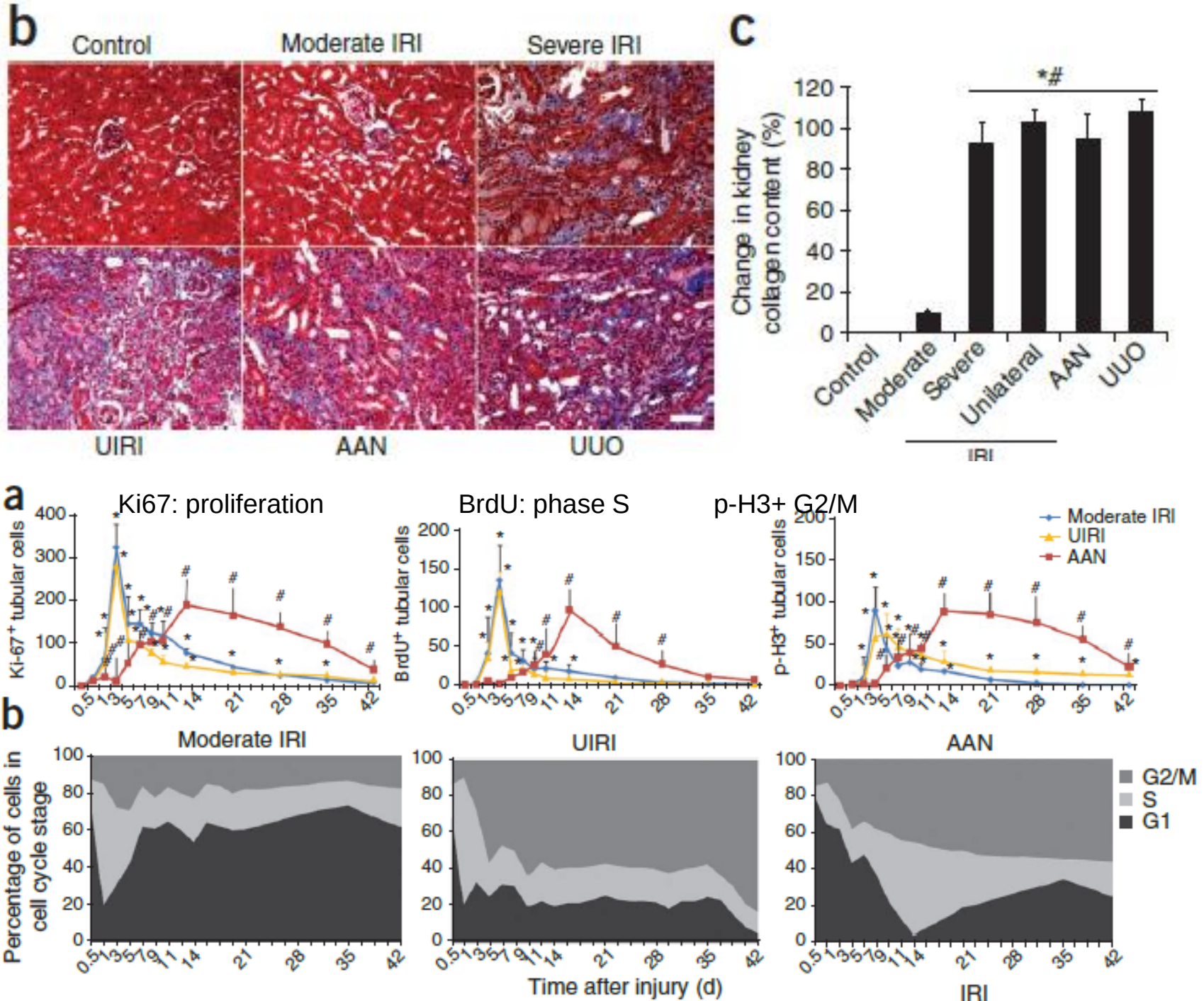
Protéinurie tubulaire
Sédiment U inactif

Traitement au long cours: Cyclosporine, Mycophénolate Mofétil, Corticoïdes

Quelle physiopathologie..?

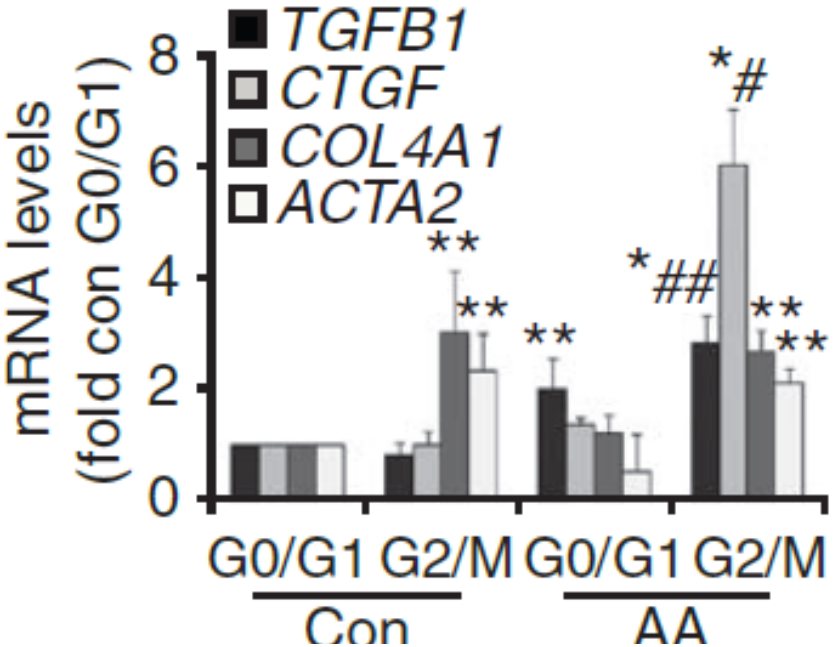
Restructuration de la chromatine

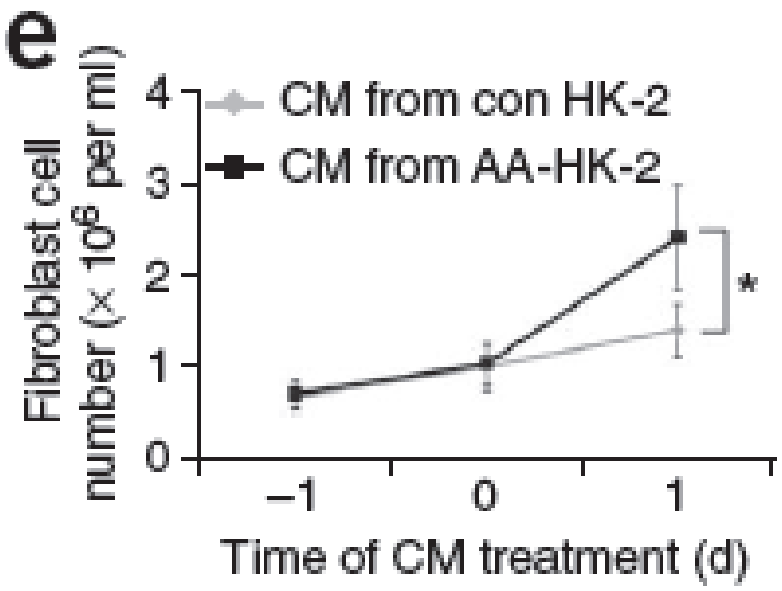


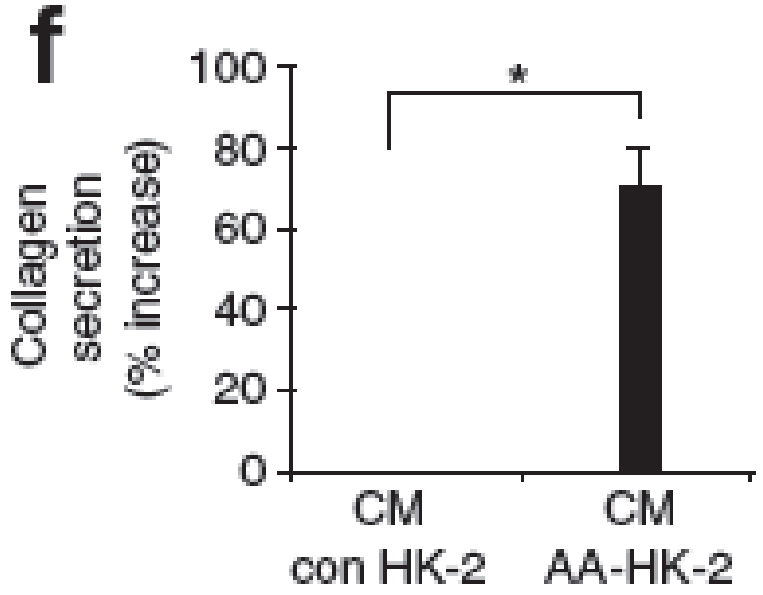

b
Control
Moderate IRI
Severe IRI
UIRI
AAN
UUO
c
Change in kidney collagen content (%)
*#
Control
Moderate
Severe
Unilateral
AAN
UUO
IRI
a
Ki67: proliferation
BrdU: phase S
p-H3+ G2/M
Ki-67+ tubular cells
BrdU+ tubular cells
p-H3+ tubular cells
Moderate IRI
UIRI
AAN
b
Moderate IRI
UIRI
AAN
Percentage of cells in cell cycle stage
G2/M
S
G1
Time after injury (d)
IRI

La production de facteurs pro-fibrogéniques par des HK2 bloquées en G2/M est augmentée.

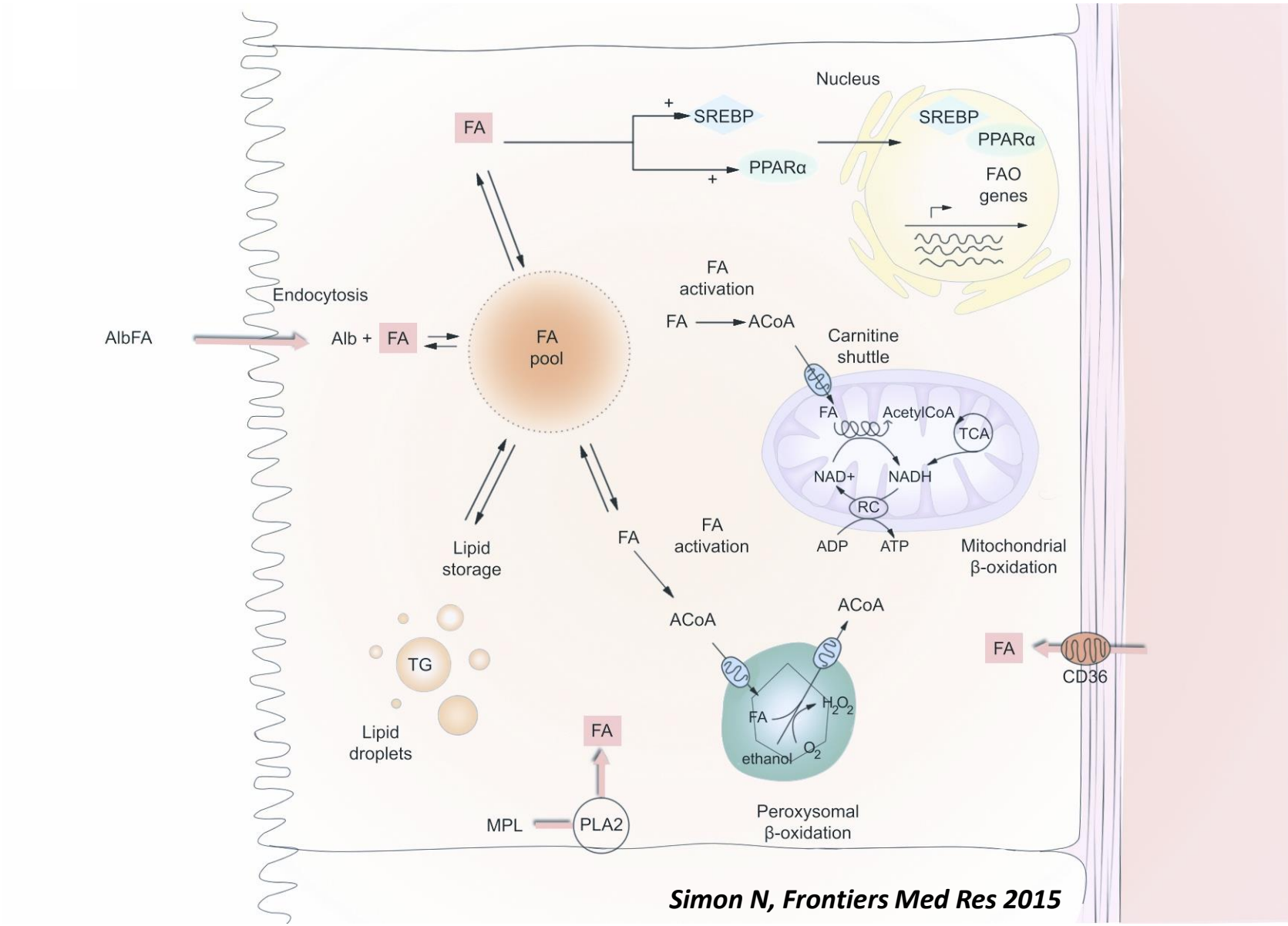
Les fibroblastes exposés au surnageant d'HK2 G2/M prolifèrent plus, fabriquent plus de matrice.







La perte des fonctions épithéliales est peut-être la conséquence directe des répercussions énergétiques de l'ischémie

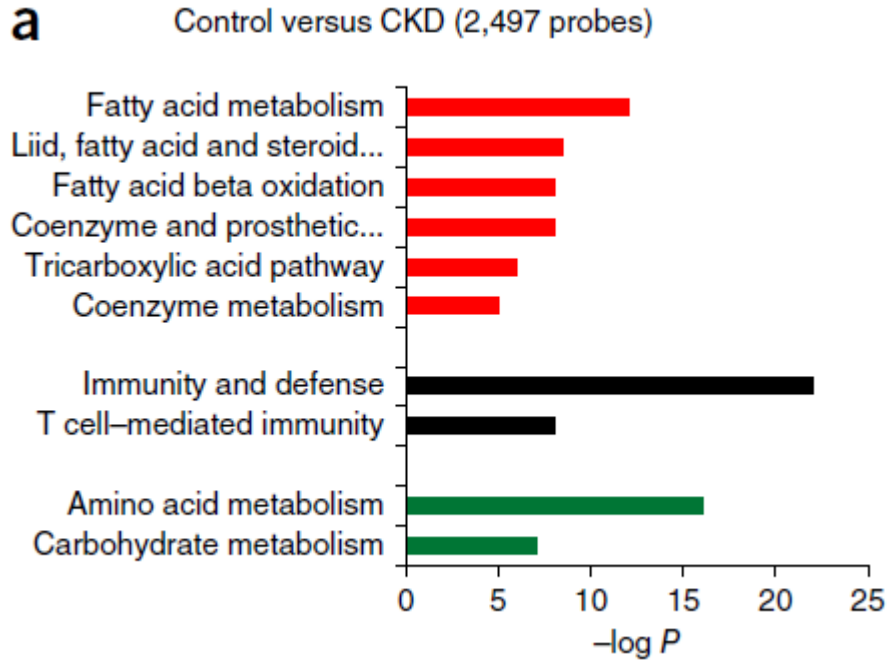


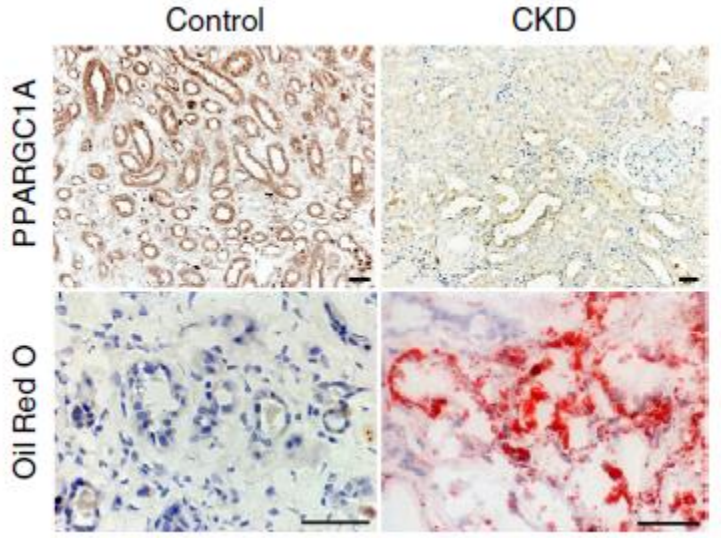
Simon N, Frontiers Med Res 2015

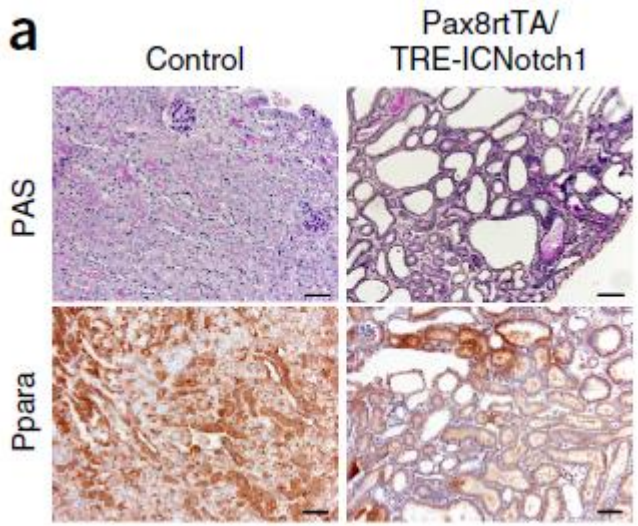
nature medicine

Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development

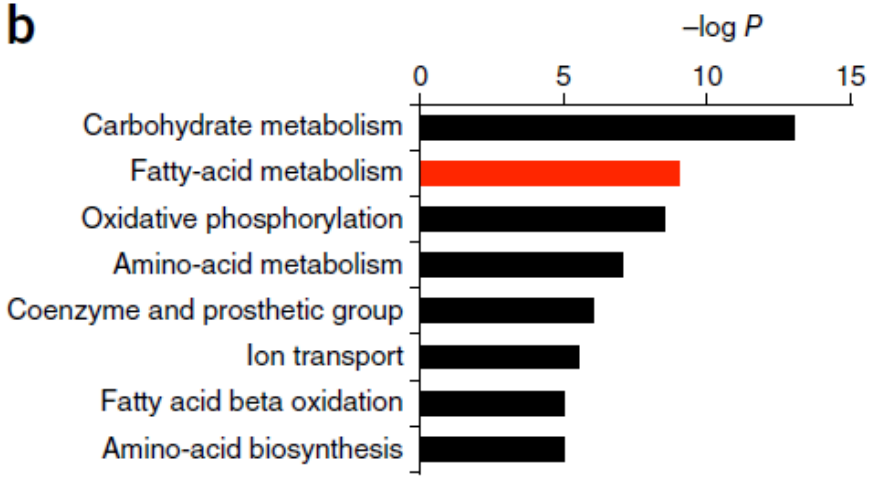
Hyun Mi Kang[1], Seon Ho Ahn[1,6], Peter Choi[1], Yi-An Ko[1], Seung Hyeok Han[1], Frank Chinga[1], Ae Seo Deok Park[1], Jianling Tao[1,6], Kumar Sharma[2], James Pullman[3], Erwin P Bottinger[4], Ira J Goldberg[5] & Katalin Susztak[1]

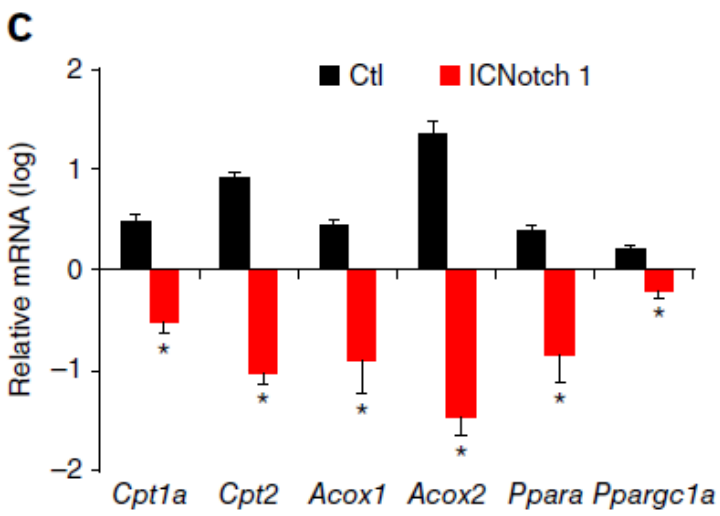


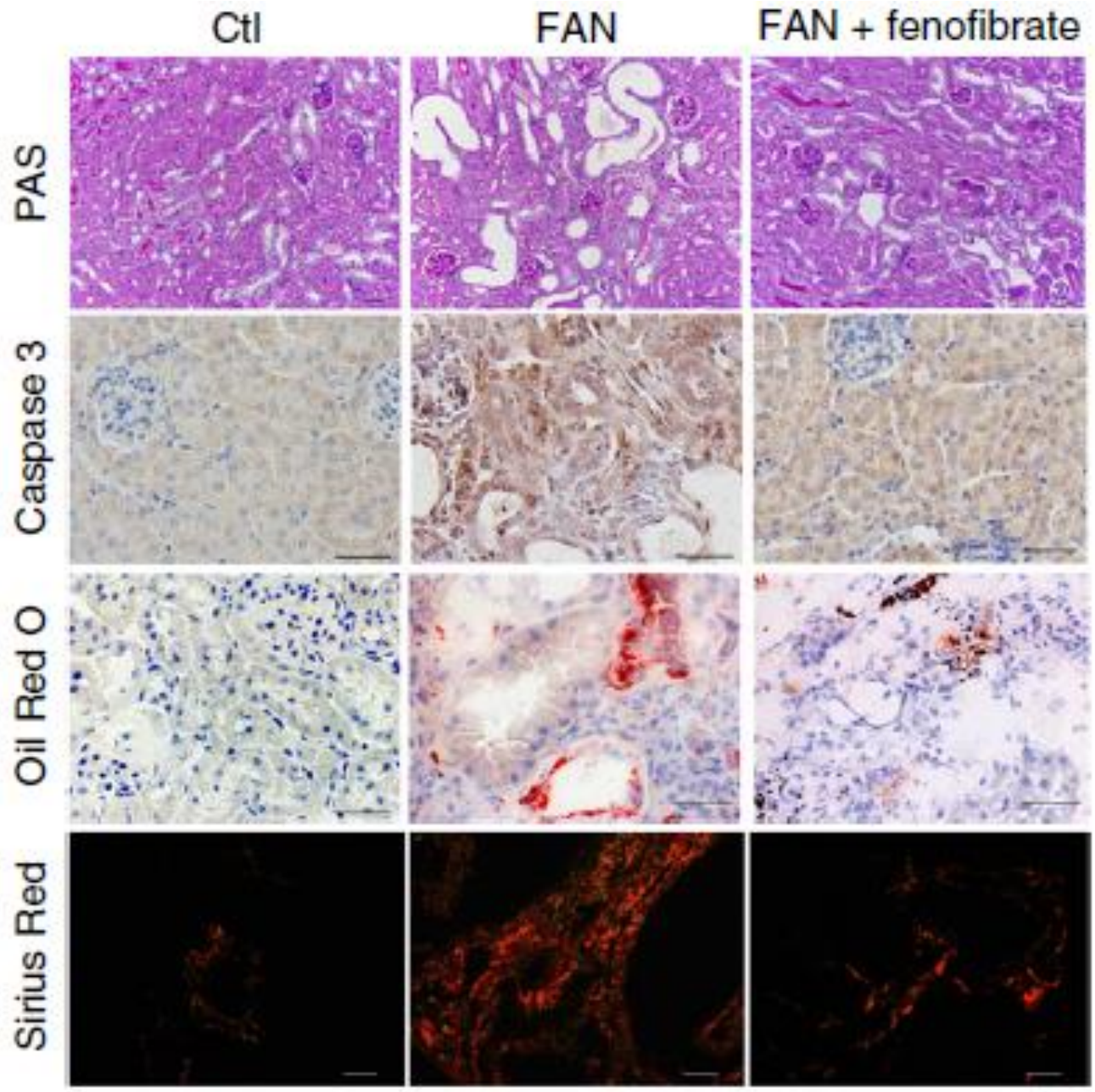




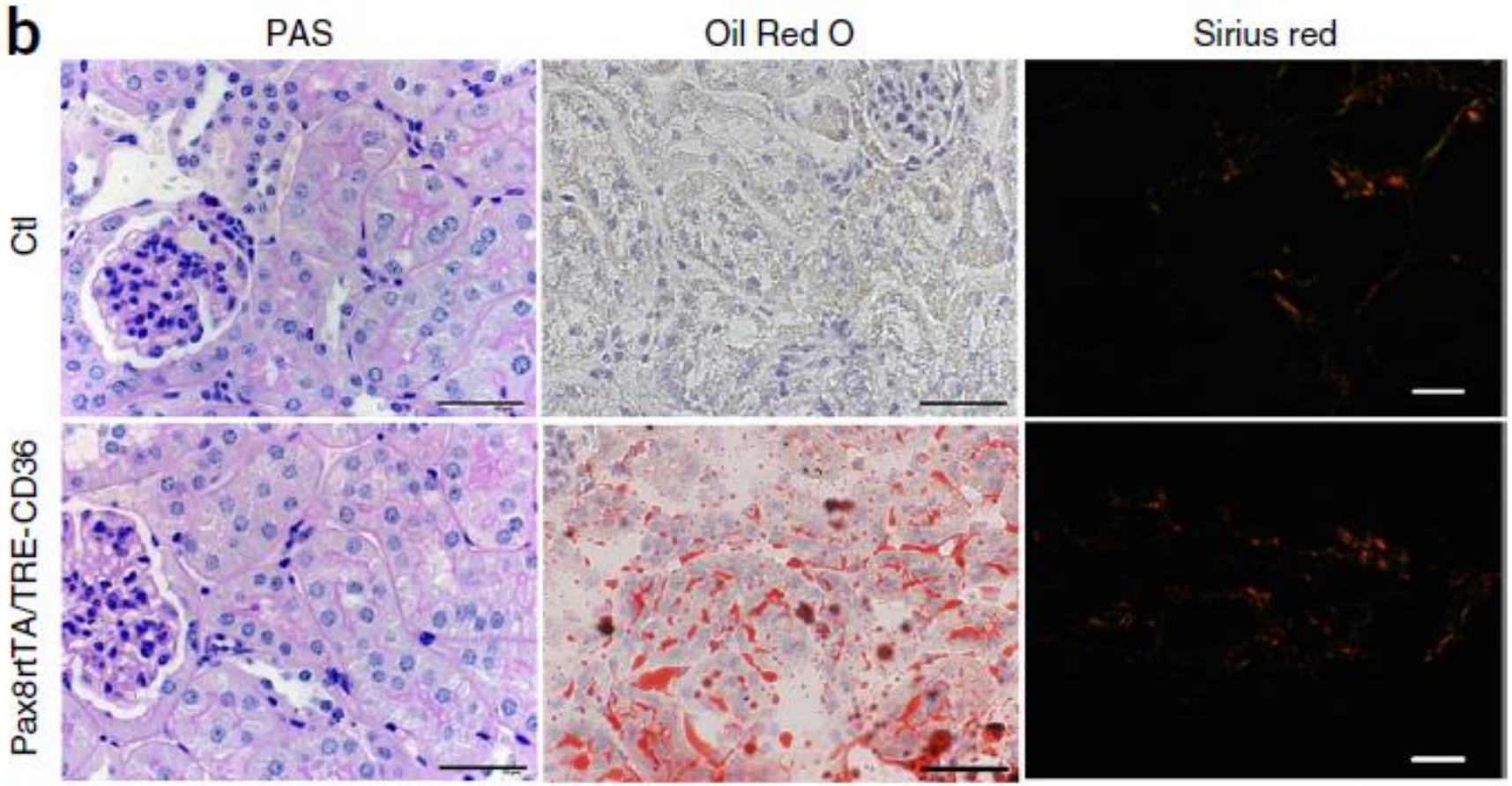
Effondrement de la FAO dans un modèle animal de fibrose rénale

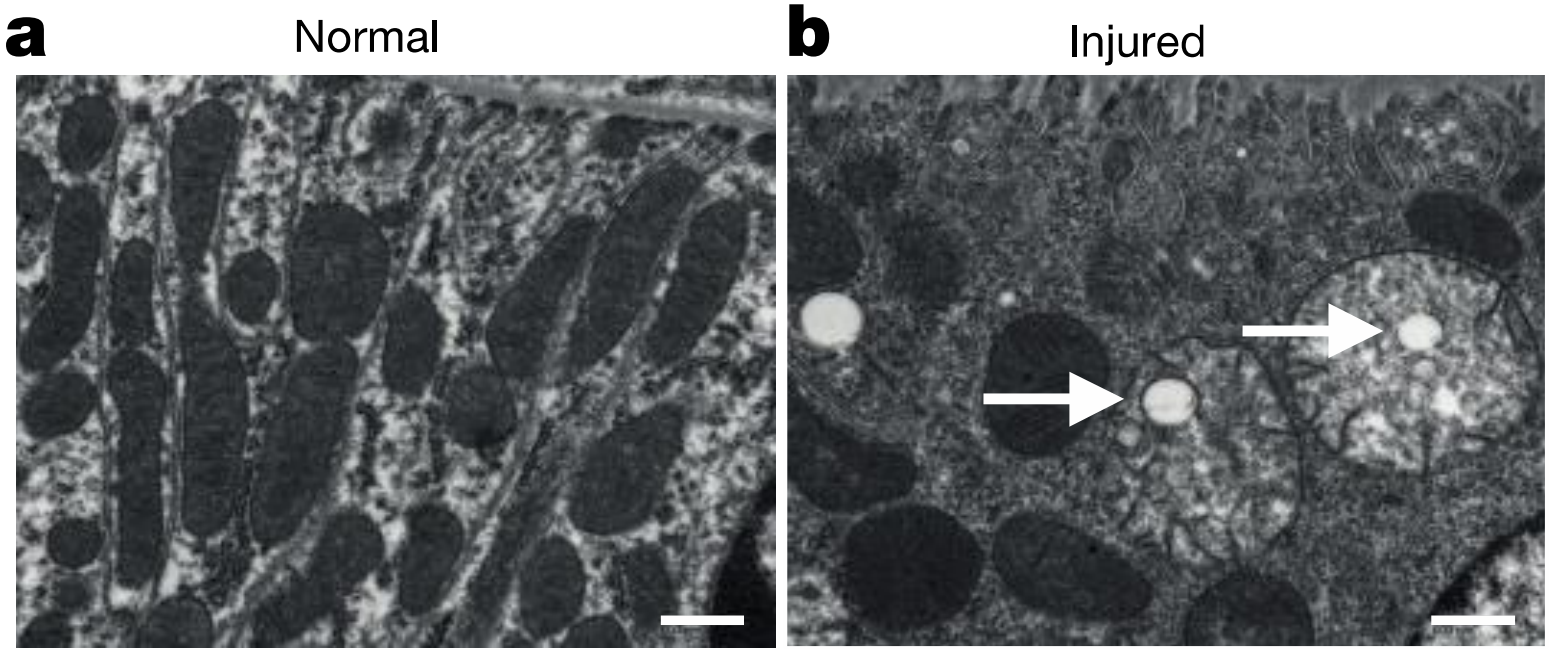





Ctl
FAN
FAN + fenofibrate
PAS
Caspase 3
Oil Red O
Sirius Red

Ce n’est pas un problème de toxicité des lipides

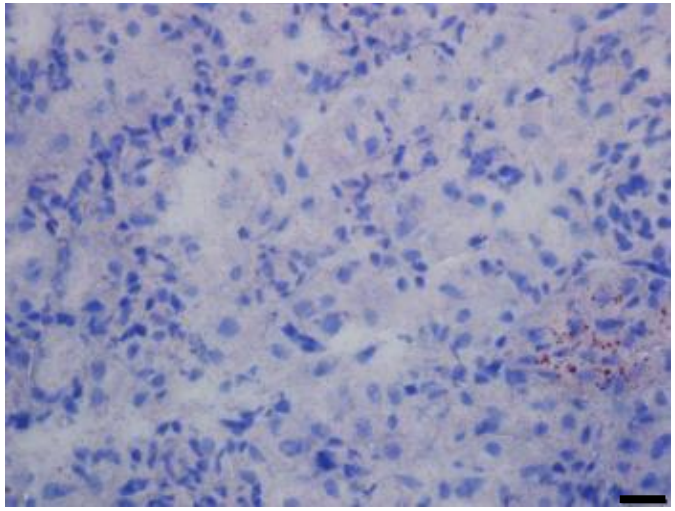




Tran MT et al., Nature 2016

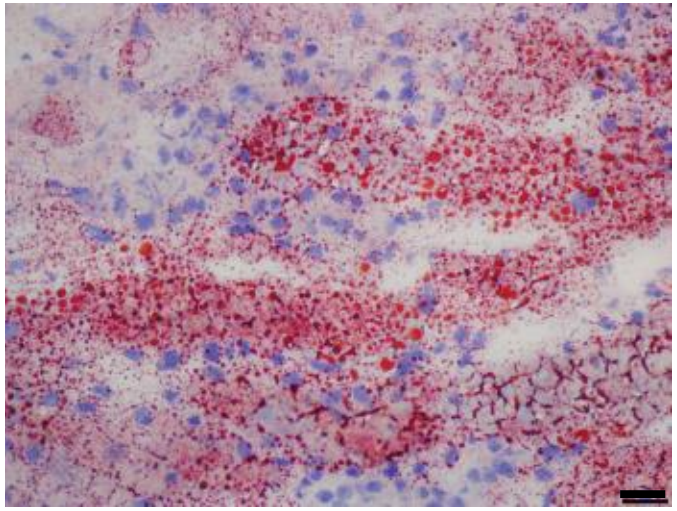
d

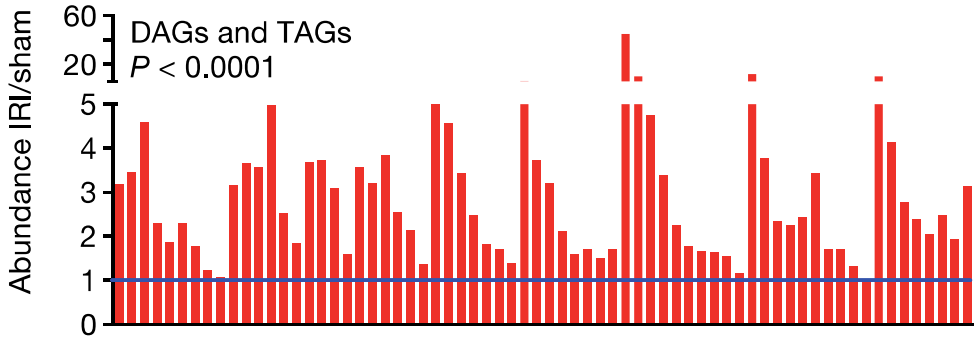
Normal



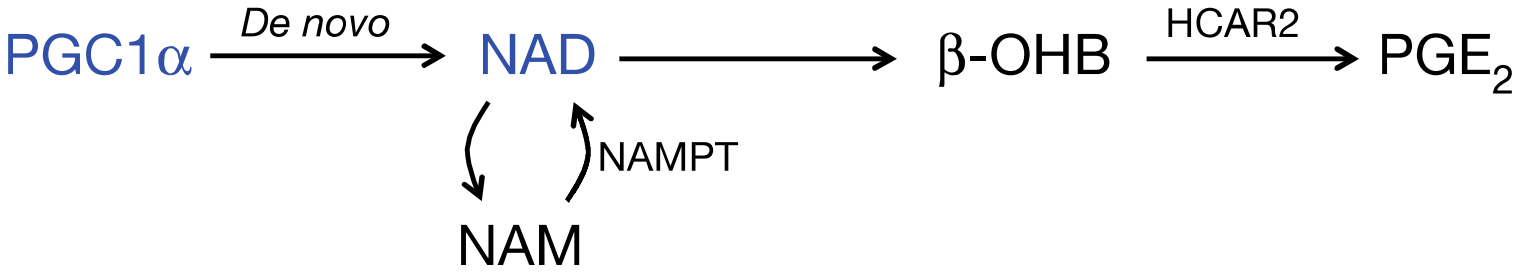
e

Injured

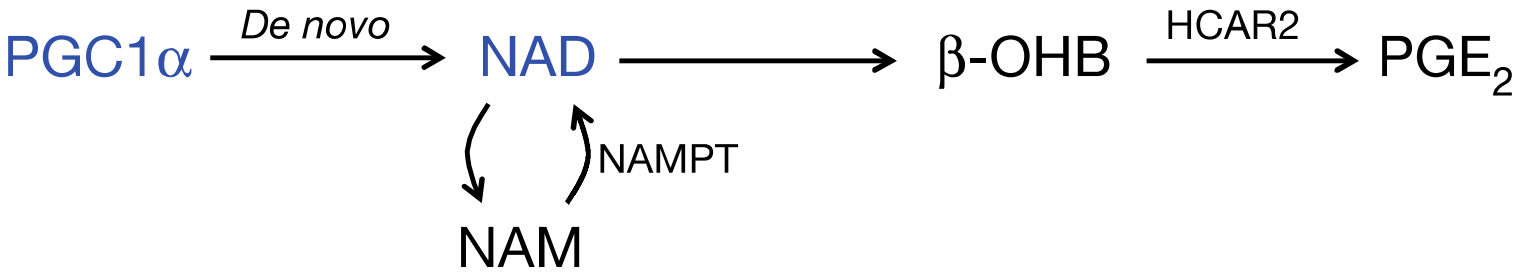


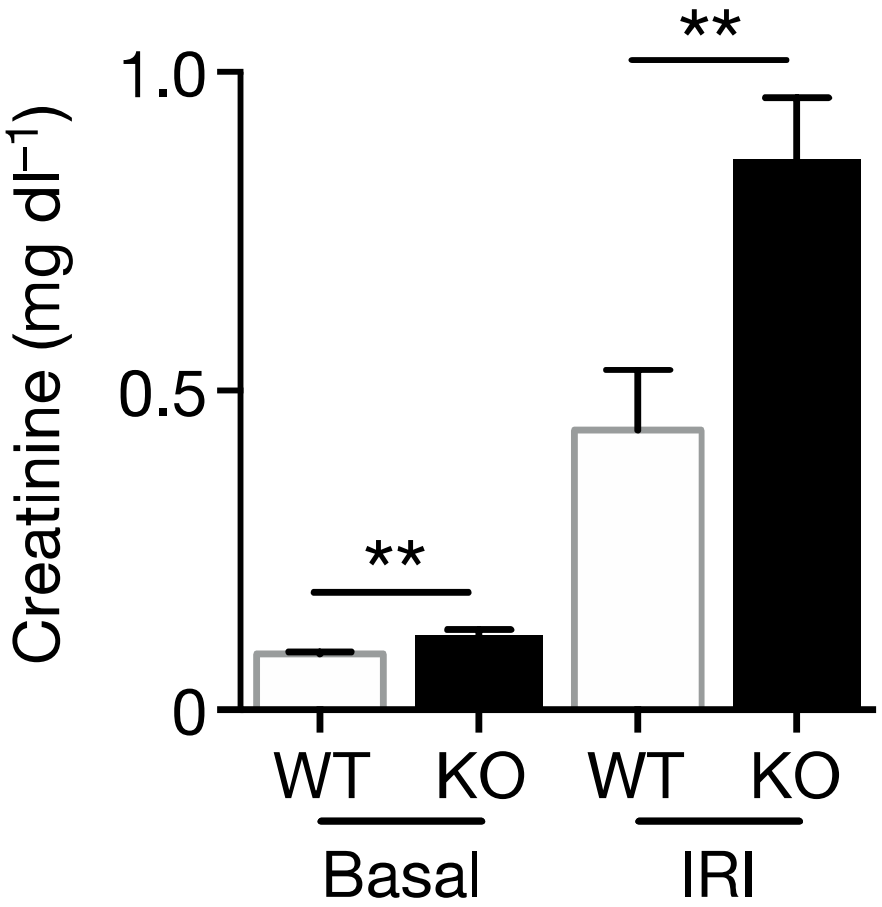


Tran MT et al., Nature 2016

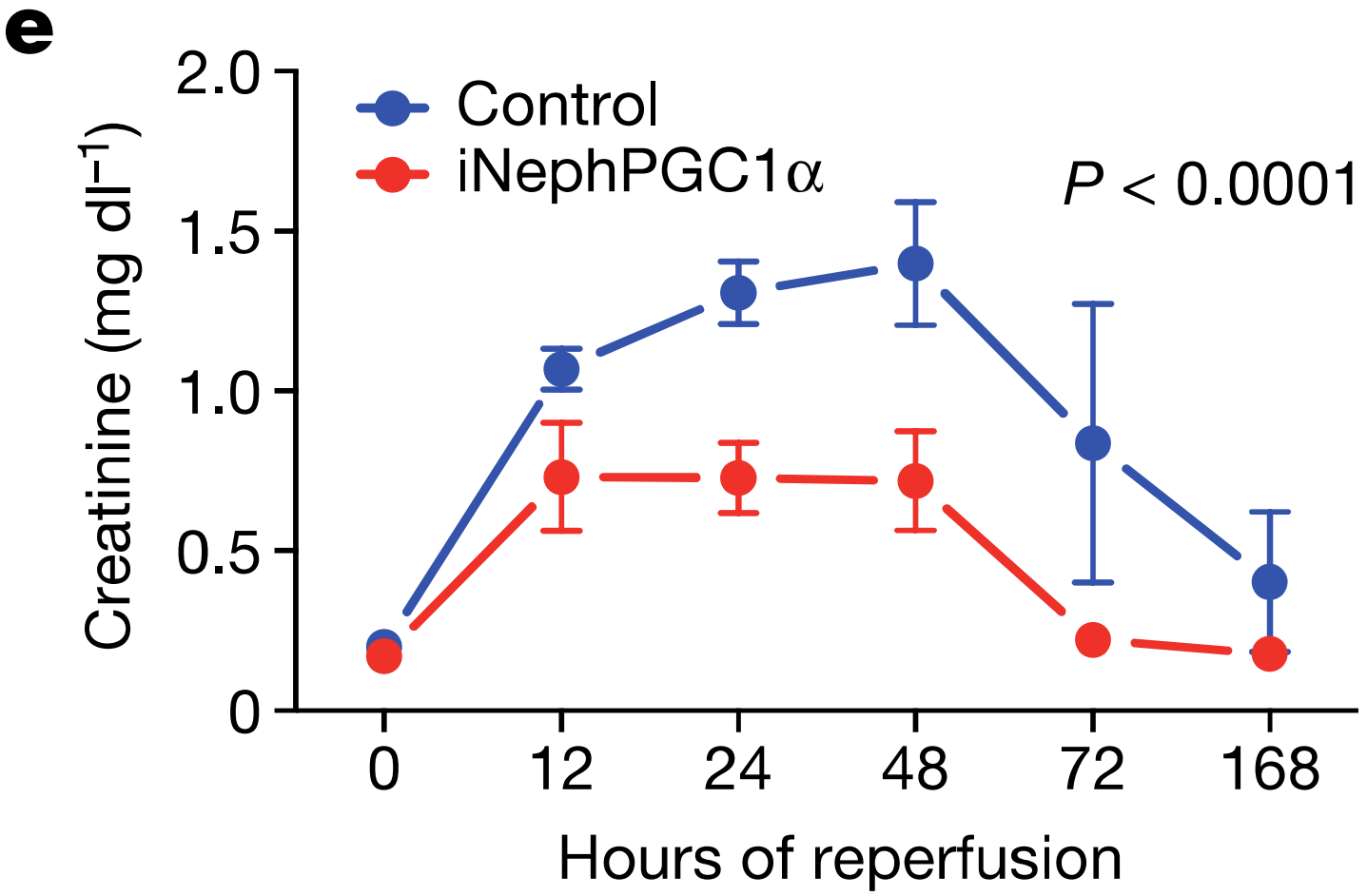


Tran MT et al., Nature 2016

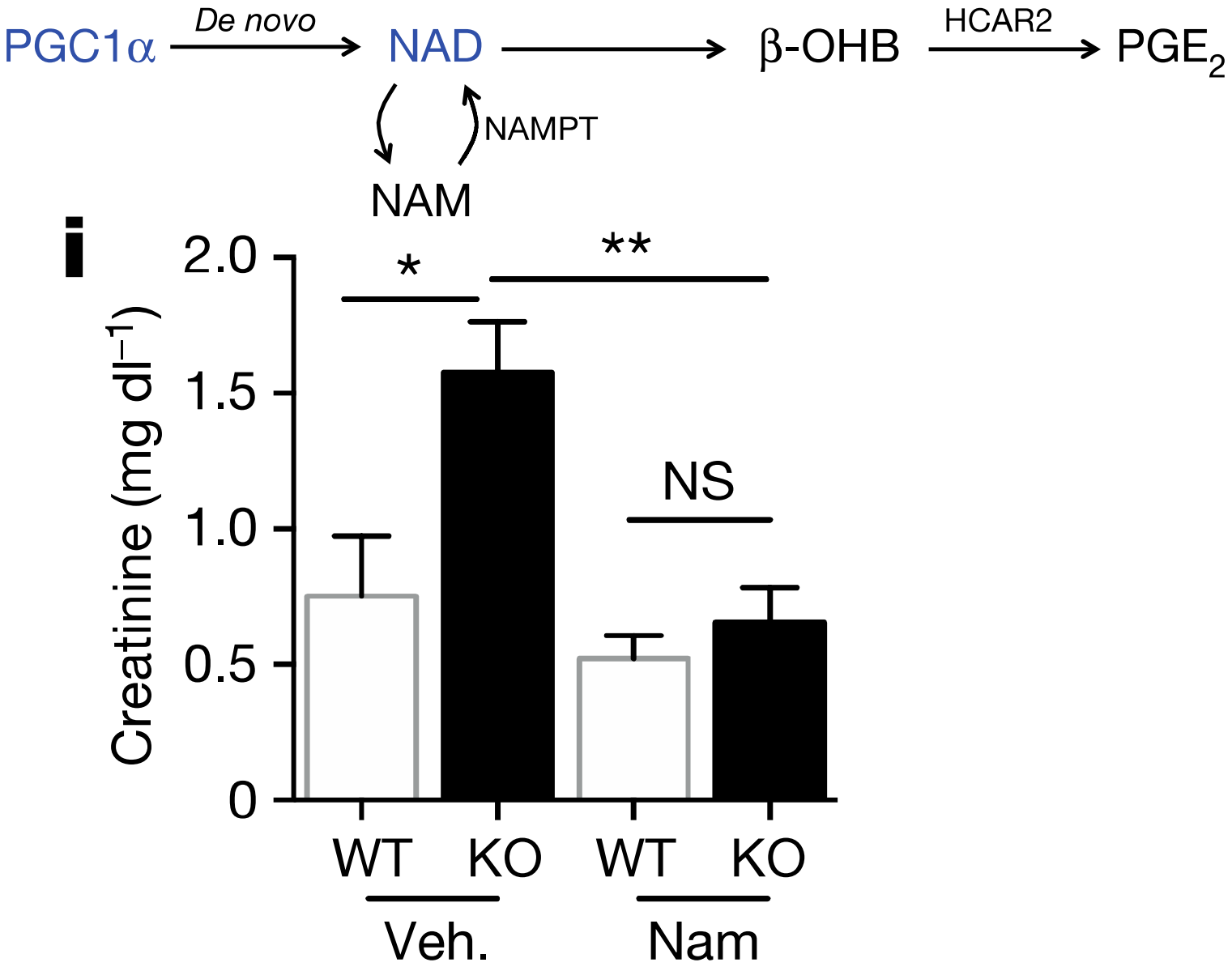




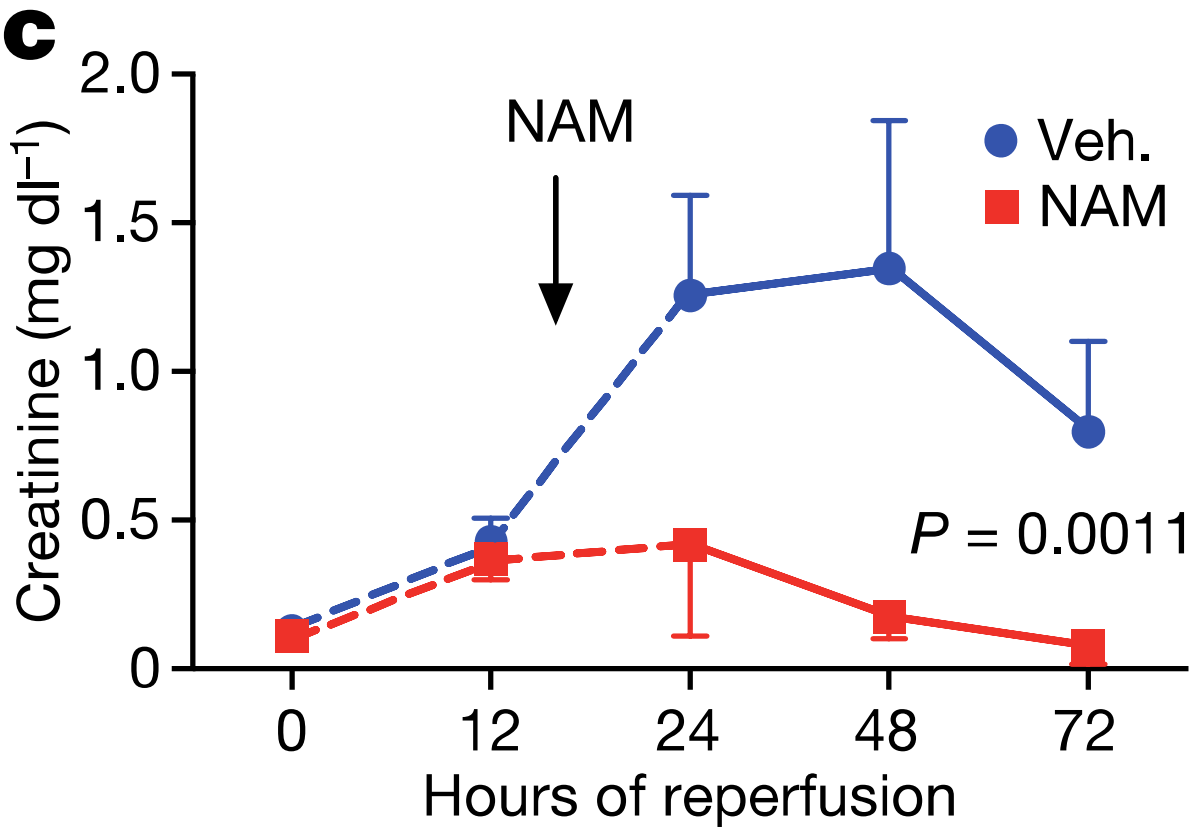
Tran MT et al., Nature 2016



Tran MT et al., Nature 2016



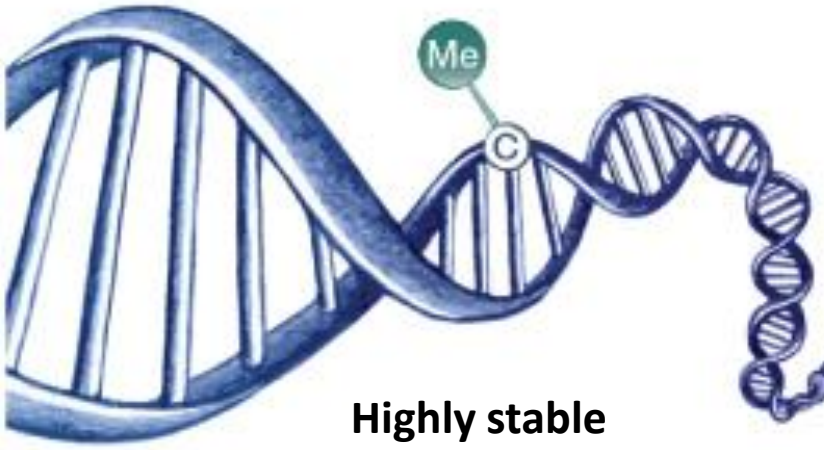
Tran MT et al., Nature 2016



Tran MT et al., Nature 2016

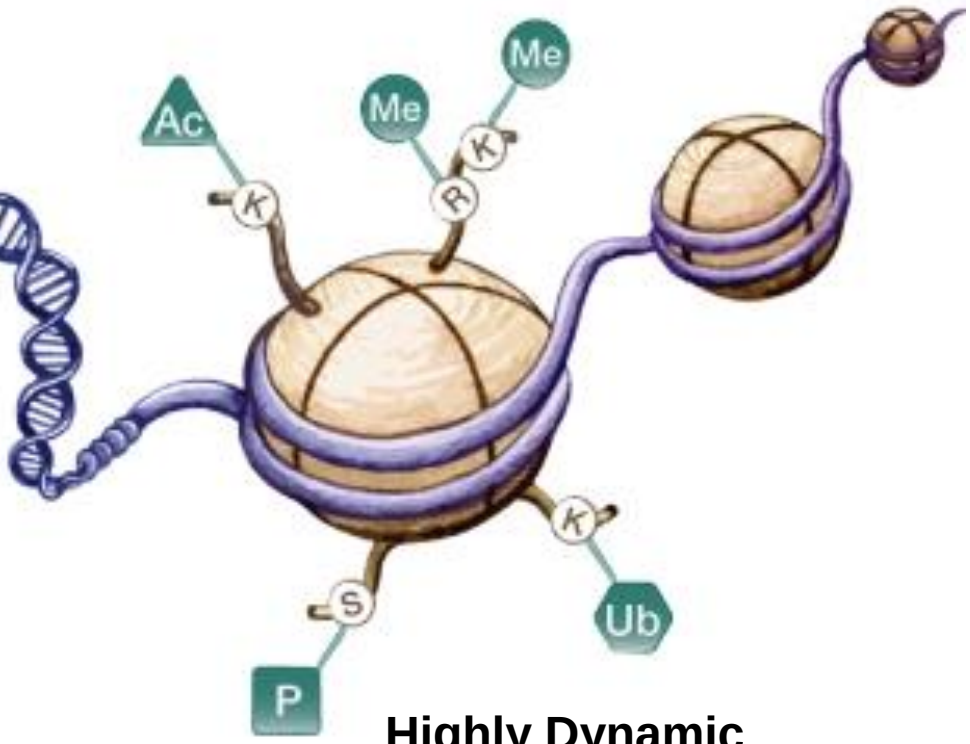
« The Triple Helix »

Methylation of Cytosine



Highly stable

Histone Modifications



Highly Dynamic

The Toadflax flower: one genome, two phenotypes

Wild-type

Peloric Epimutant

Peloria : *greek* for « Monster »

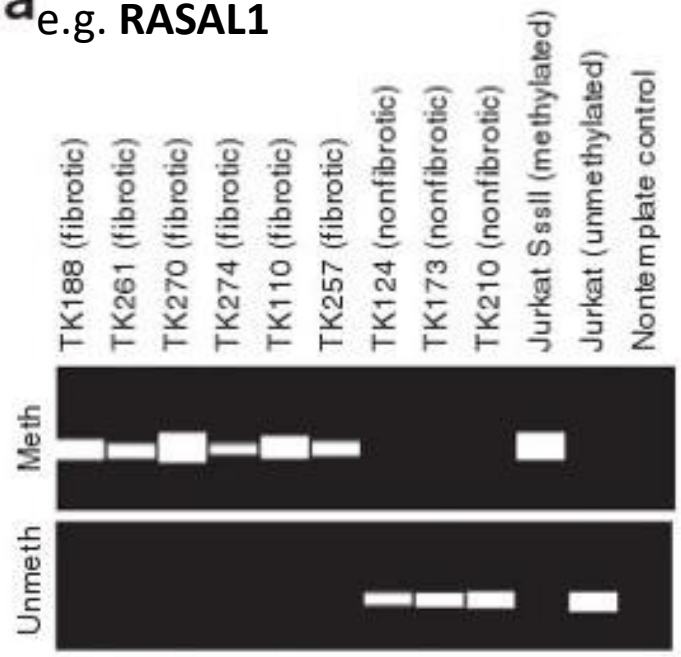
Linnaeus: "This is certainly no less remarkable than if a cow were to give birth to a calf with a wolf's head,"

Genome wide analysis of methylation profile in fibroblasts isolated from normal vs fibrotic human kidneys

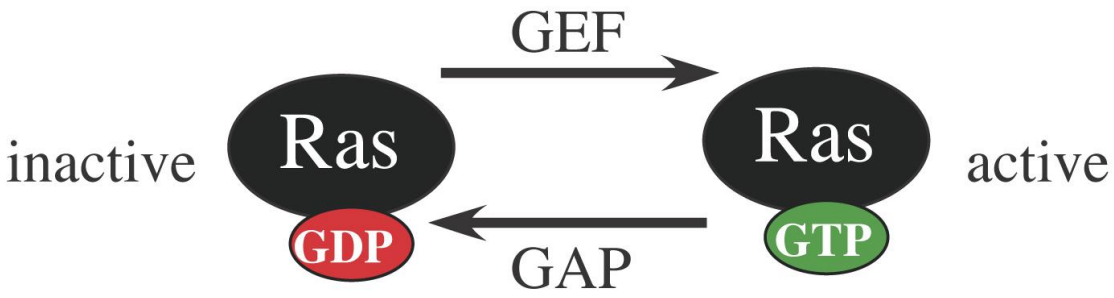
12 genes were found to be systematically methylated in fibrotic kidneys

out of which 3 have orthologs in mice

a e.g. **RASAL1**



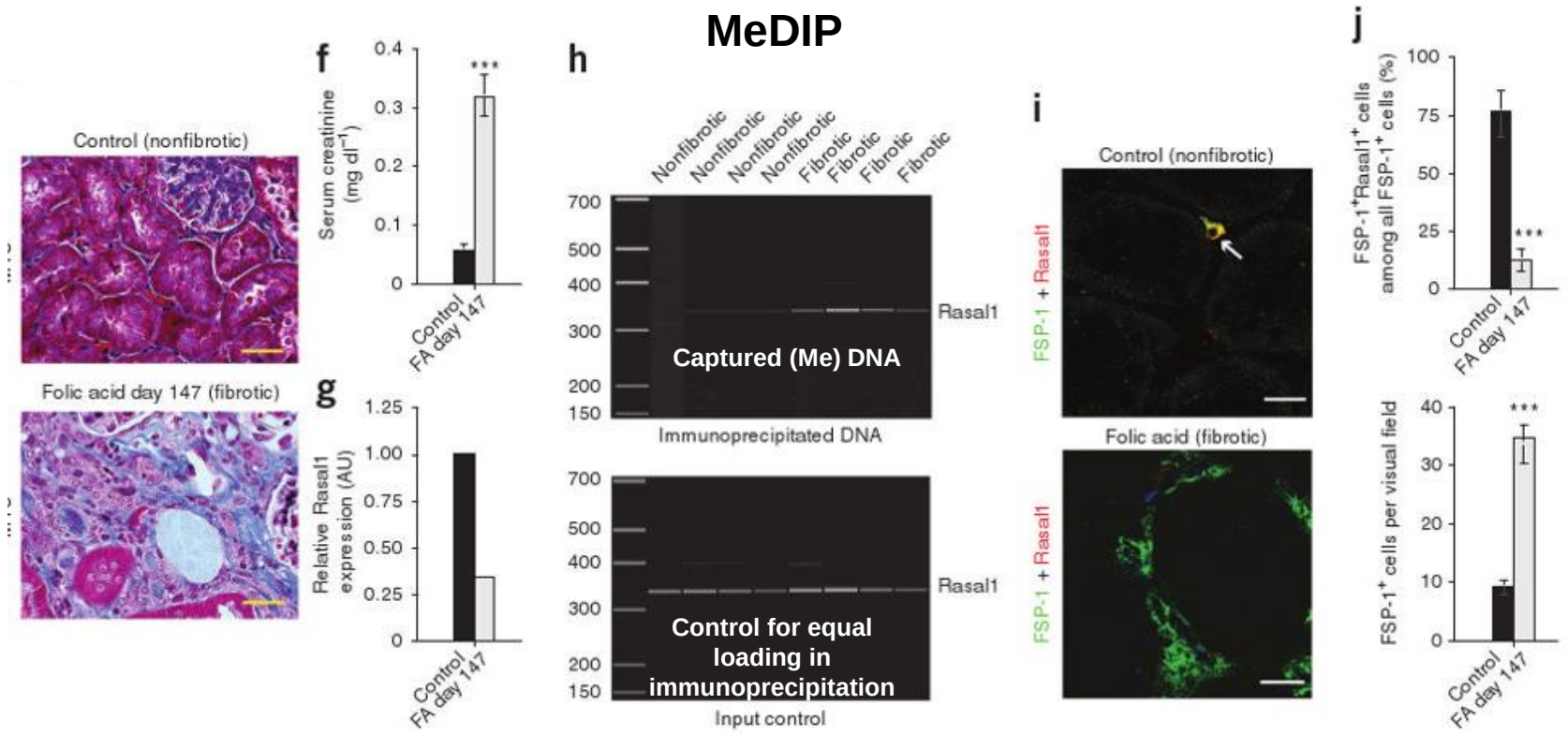
Méthylation of RASAL1 In fibroblasts extracted from fibrotic kidneys



RASAL1 is a GAP protein

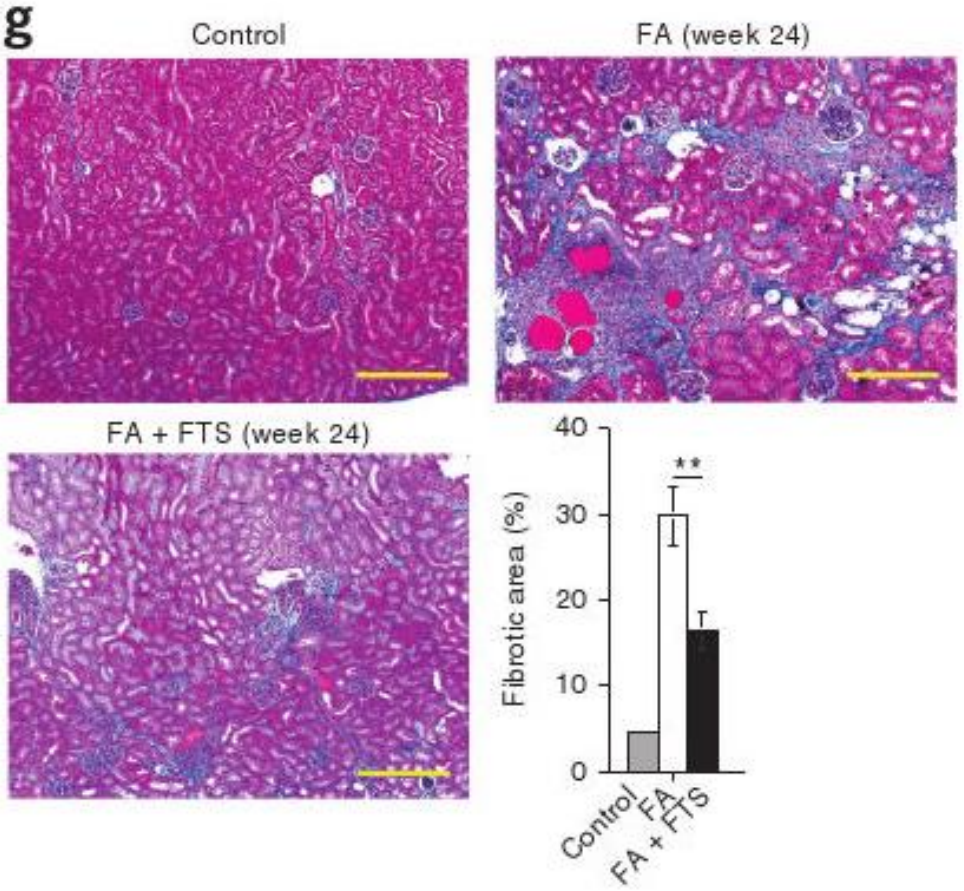
Bechtel W et al, Nat Med 2010

RASAL1 promoter is methylated in myofibroblasts from injured kidneys



Bechtel W et al, Nat Med 2010

RAS inhibitors are potentially anti-fibrotic drugs



Bechtel W et al, Nat Med 2010

CONCLUSIONS

Après un épisode d'AKI,
l'épithélium tubulaire
et les fibroblastes interstitiels
ont un comportement fibrogénique
(G2/M, FAO, RASAL1)

10 ans après: 15% des patients sont en dialyse

L'AKI est un facteur de risque
MAJEUR d'ESRD RAPIDE