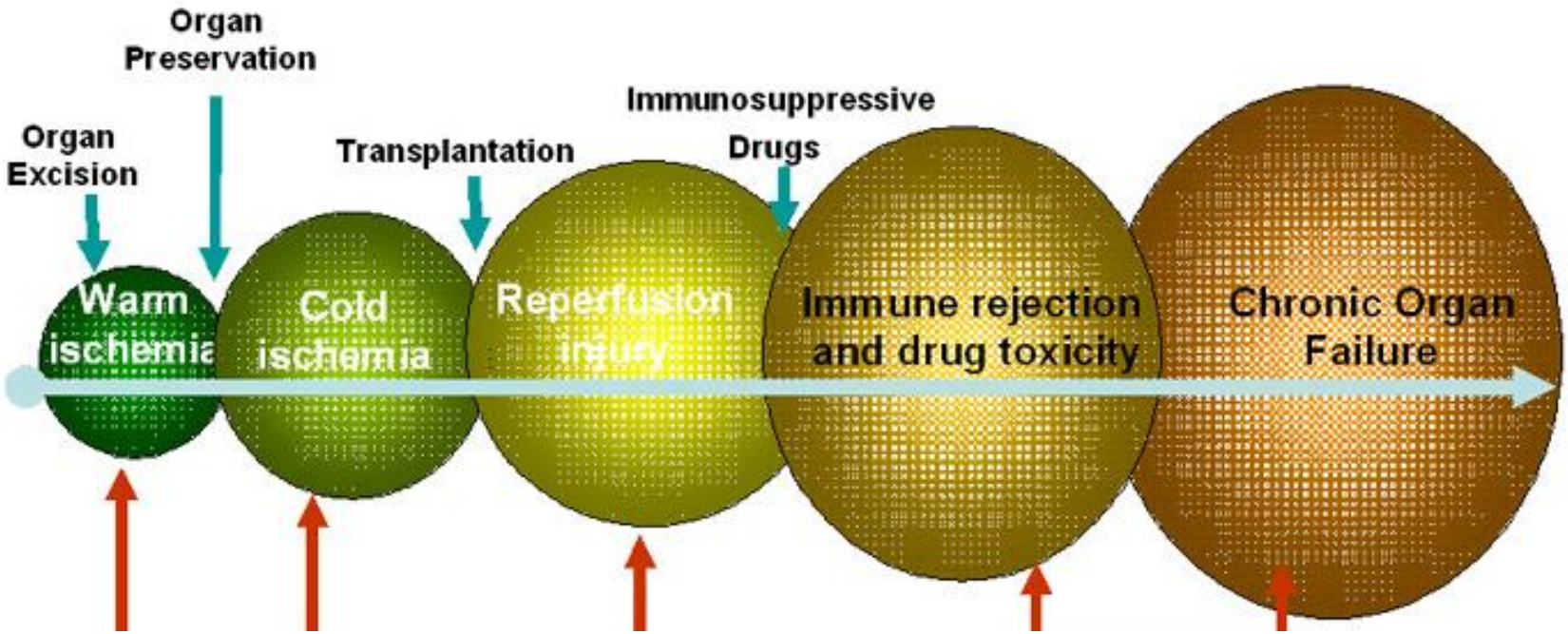
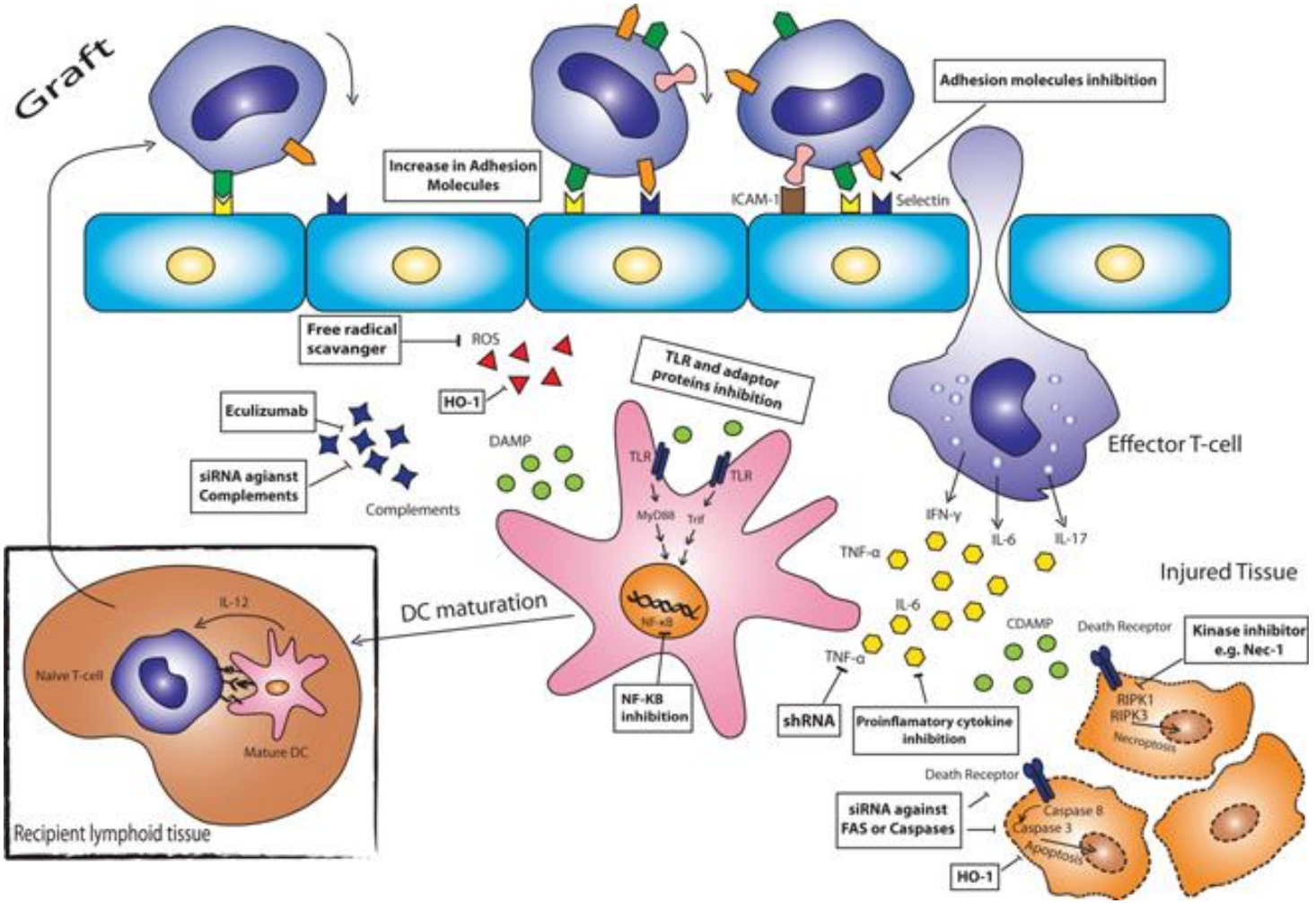
Il danno da Ischemia Riperfusione

Giuseppe Castellano, M.D., Ph.D,
University of Bari
Department of Emergency and Organ Transplantation
Nephrology, Dialysis and Transplant Unit

Tissue injury in kidney Transplantation



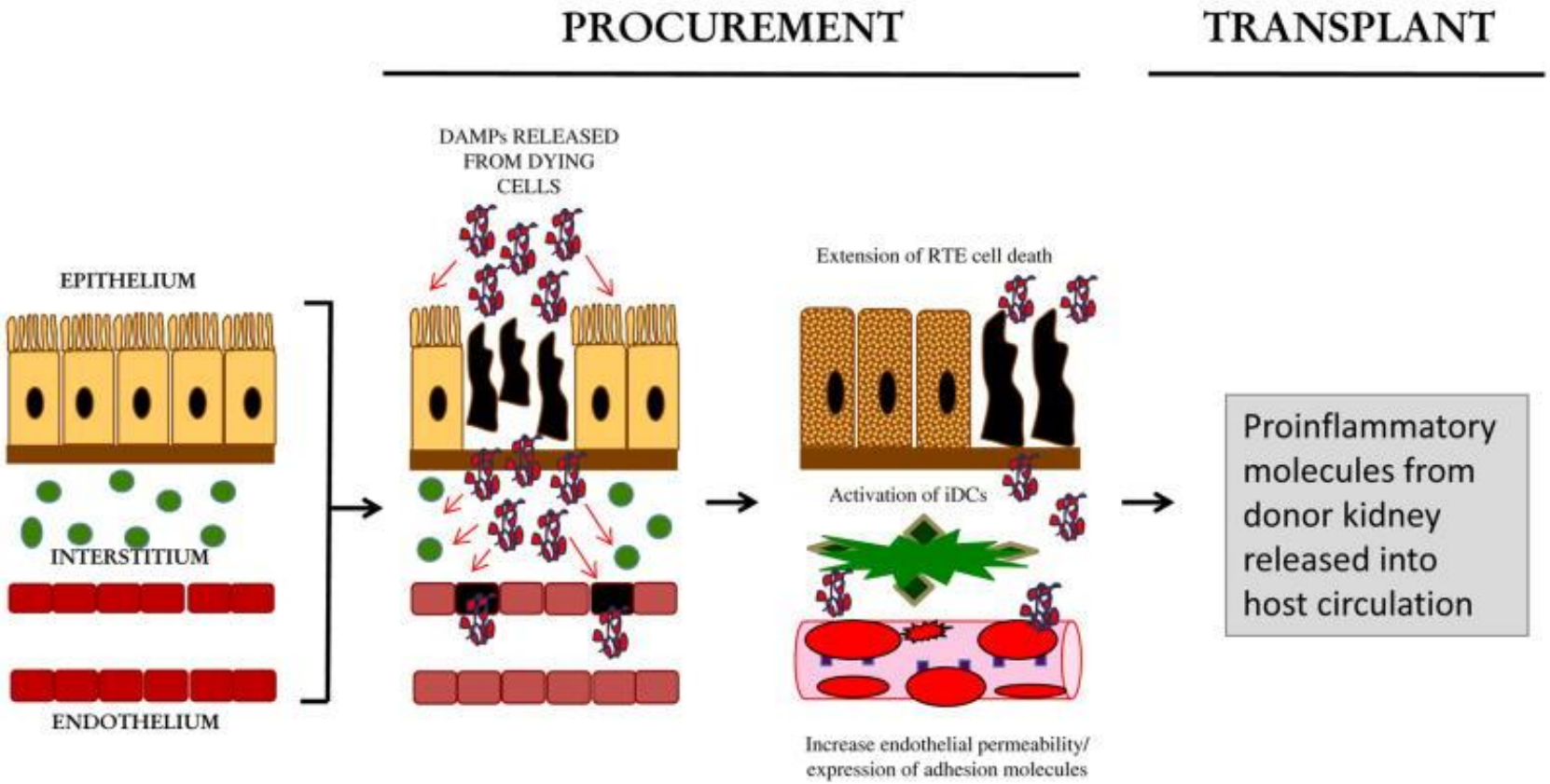
Emerging Therapies Targeting Intra-Organ Inflammation in Transplantation



American Journal of Transplantation
Volume 15, Issue 2, pages 305-311, 22 JAN 2015 DOI: 10.1111/ajt.13073
http://onlinelibrary.wiley.com/doi/10.1111/ajt.13073/full#ajt13073-fig-0001

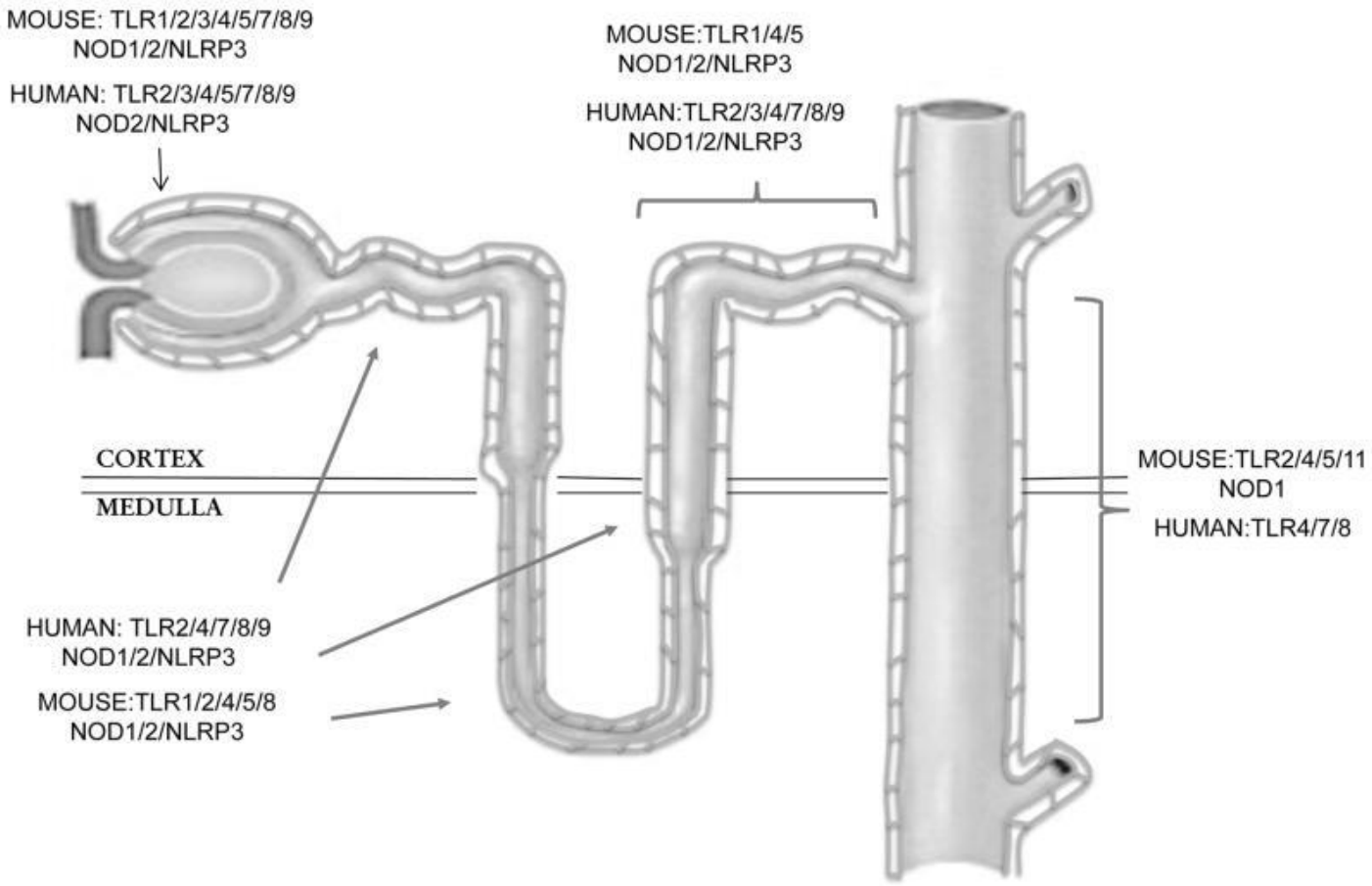
Solhjlou 2015

Consequences of donor organ ischemia on innate immune activation



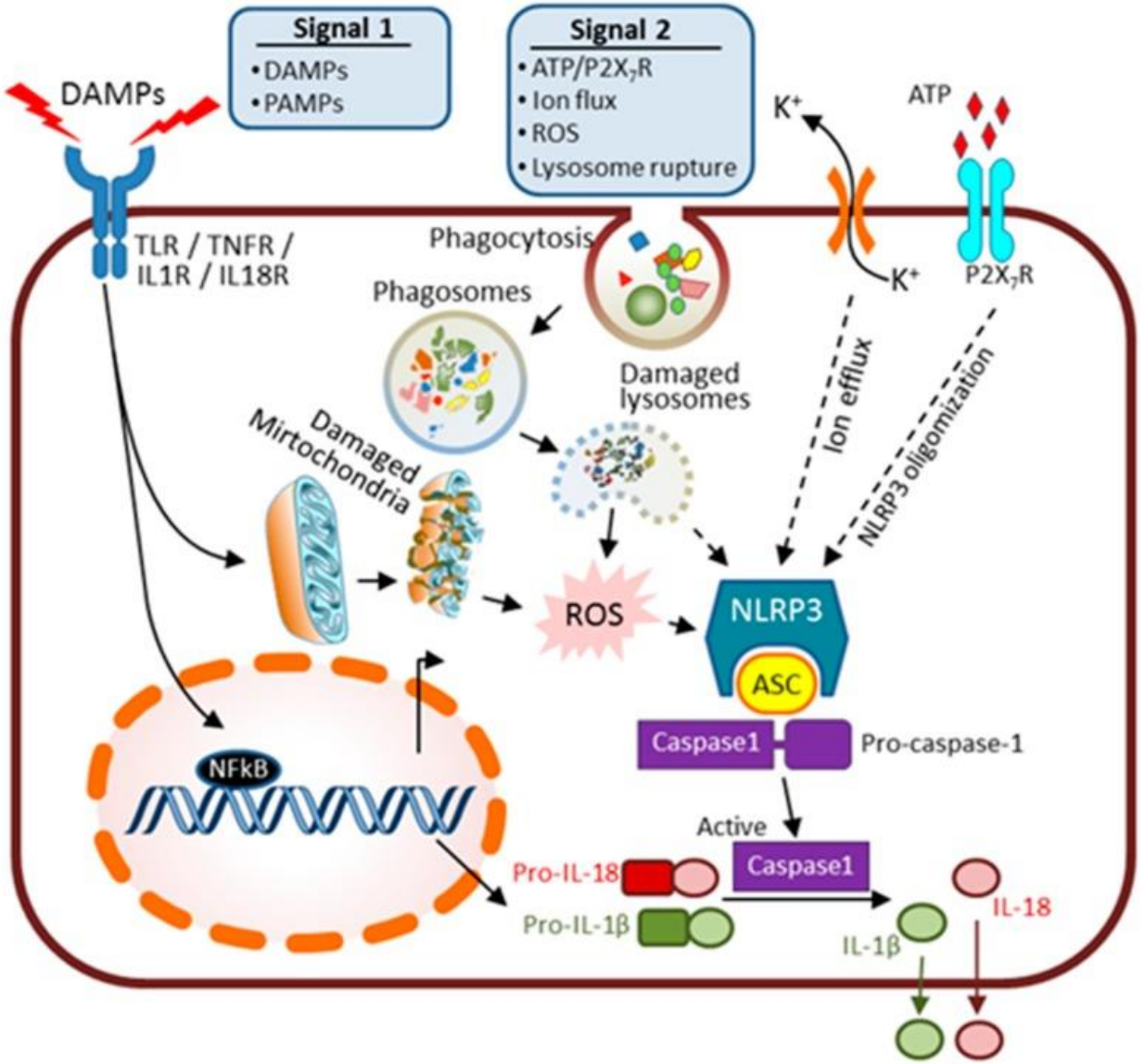
DB McKay 2016

Pattern recognition receptors expressed throughout the nephron



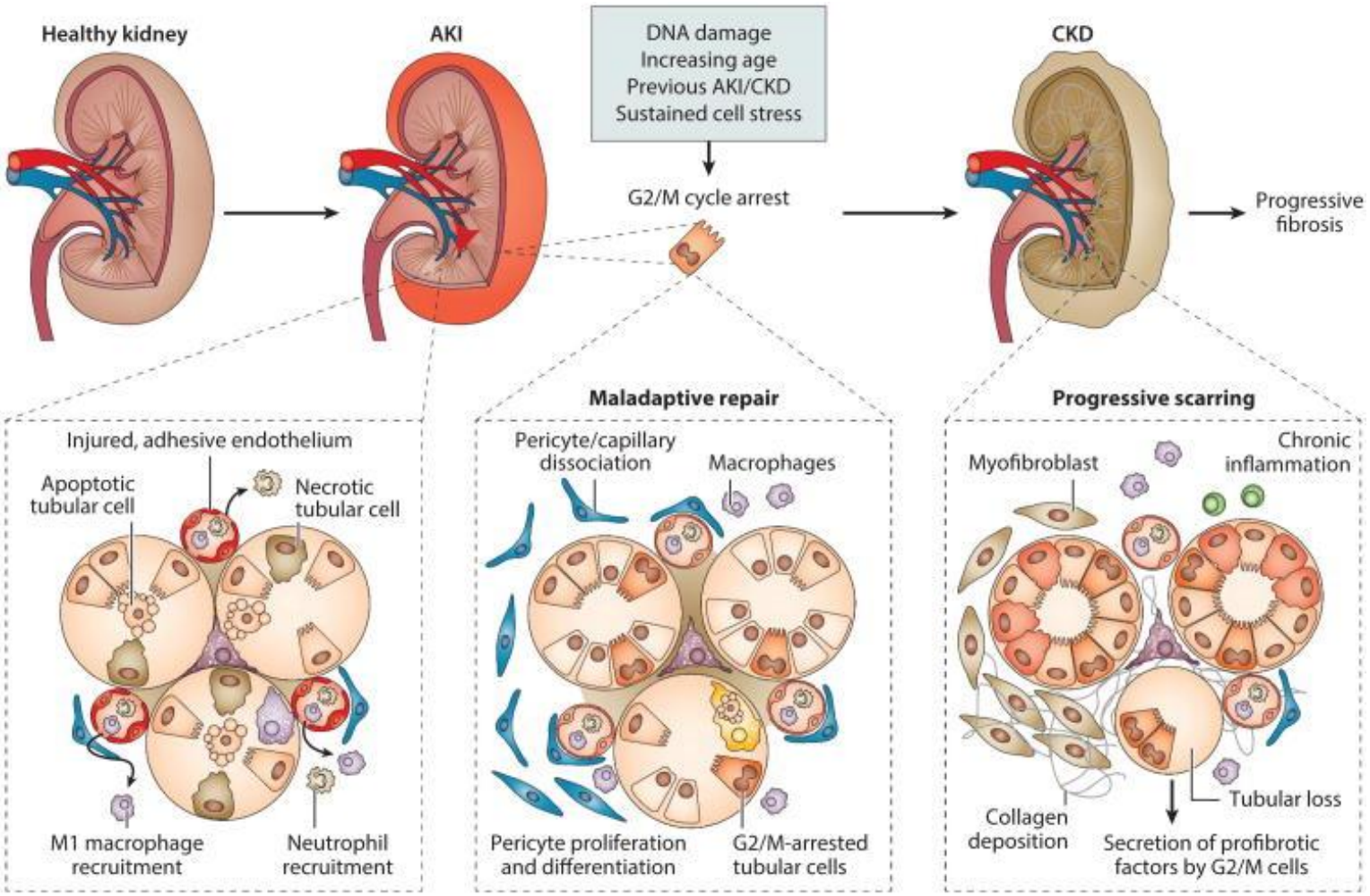
DB McKay 2016

Inflammasome signaling in AKI



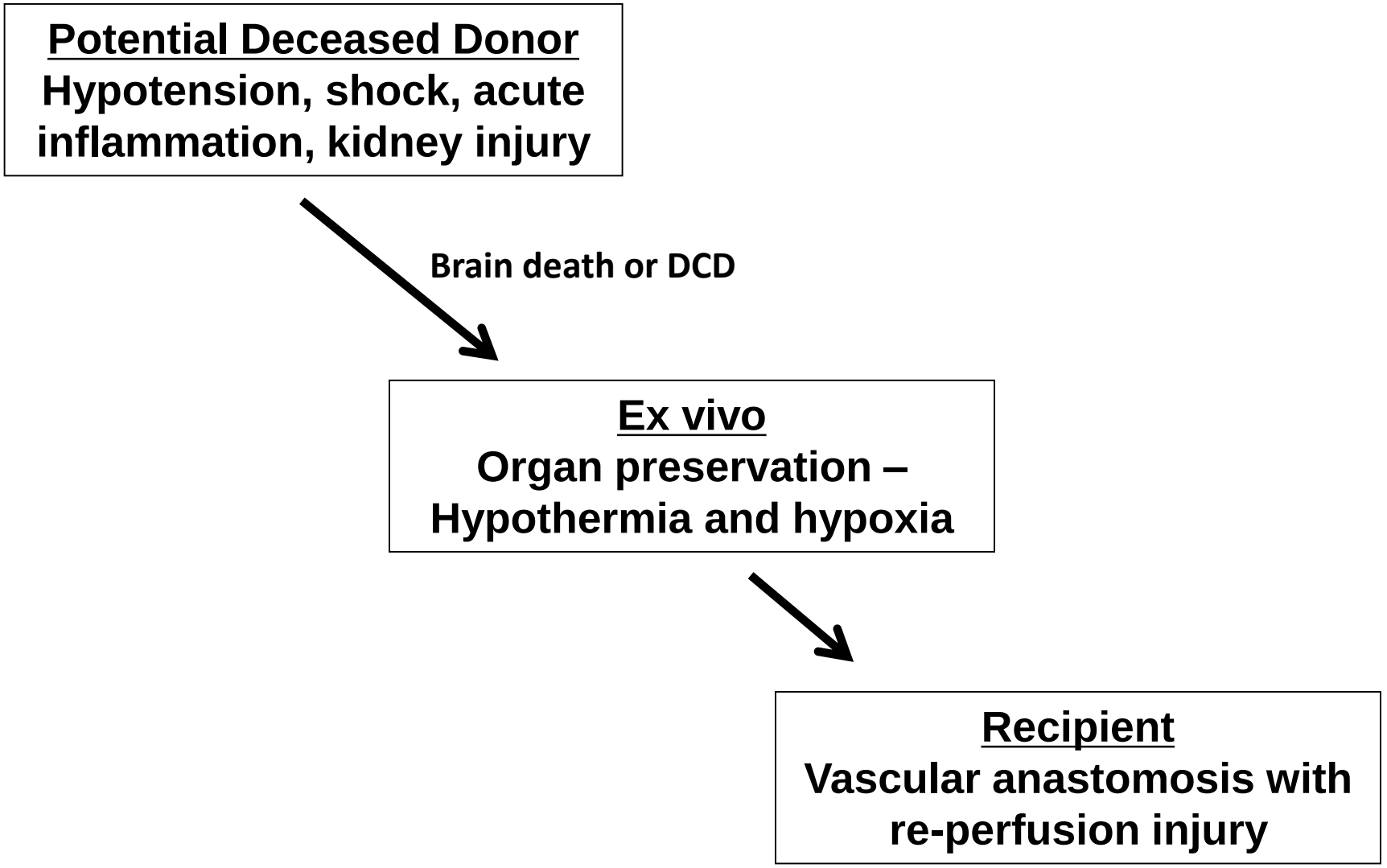
Lin PH 2016

Maladaptive repair following acute kidney injury (AKI)

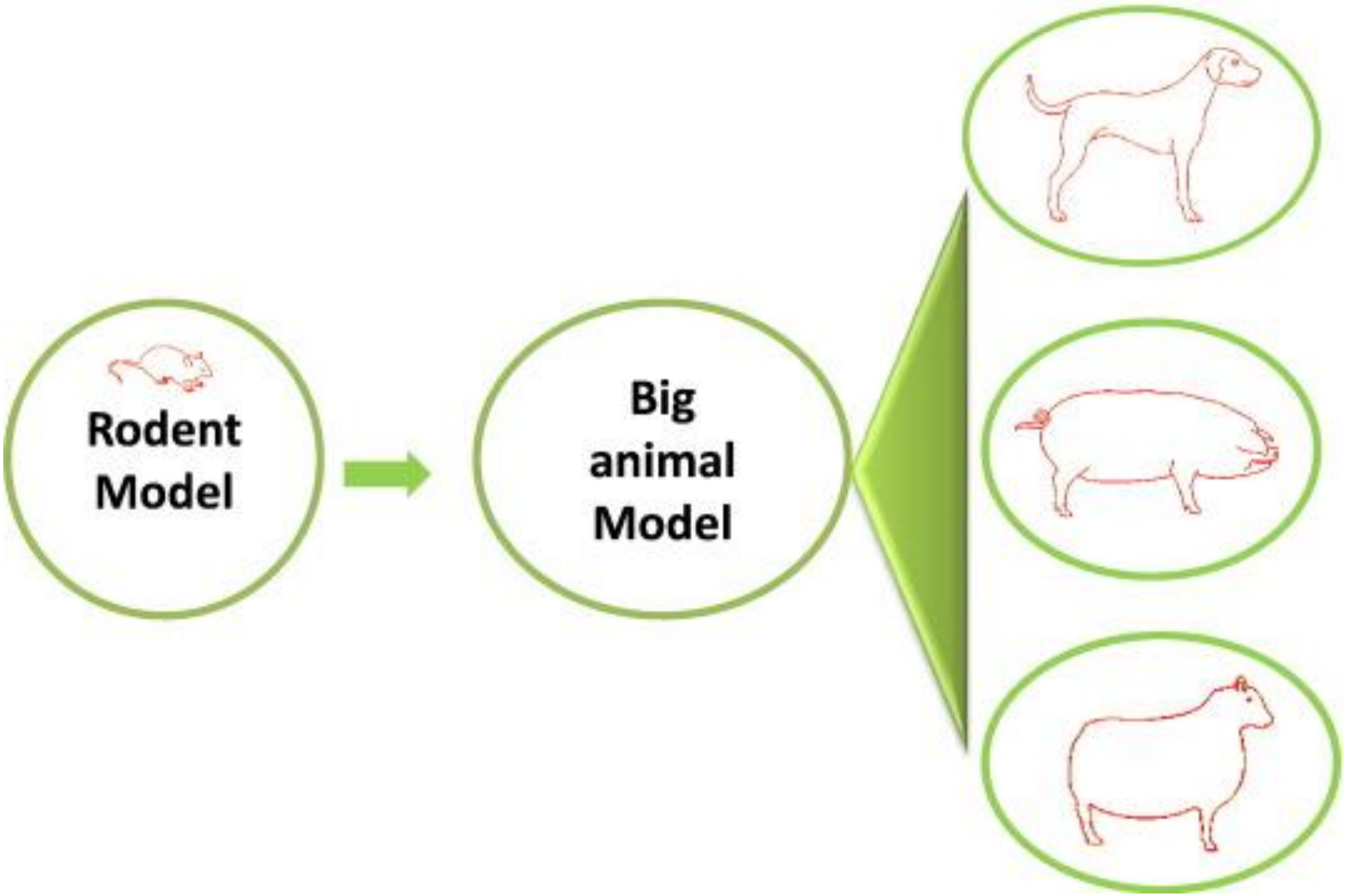


Bonventre 2016

Deceased Donor Kidney Transplantation: A Model of Ischemia-Reperfusion Injury

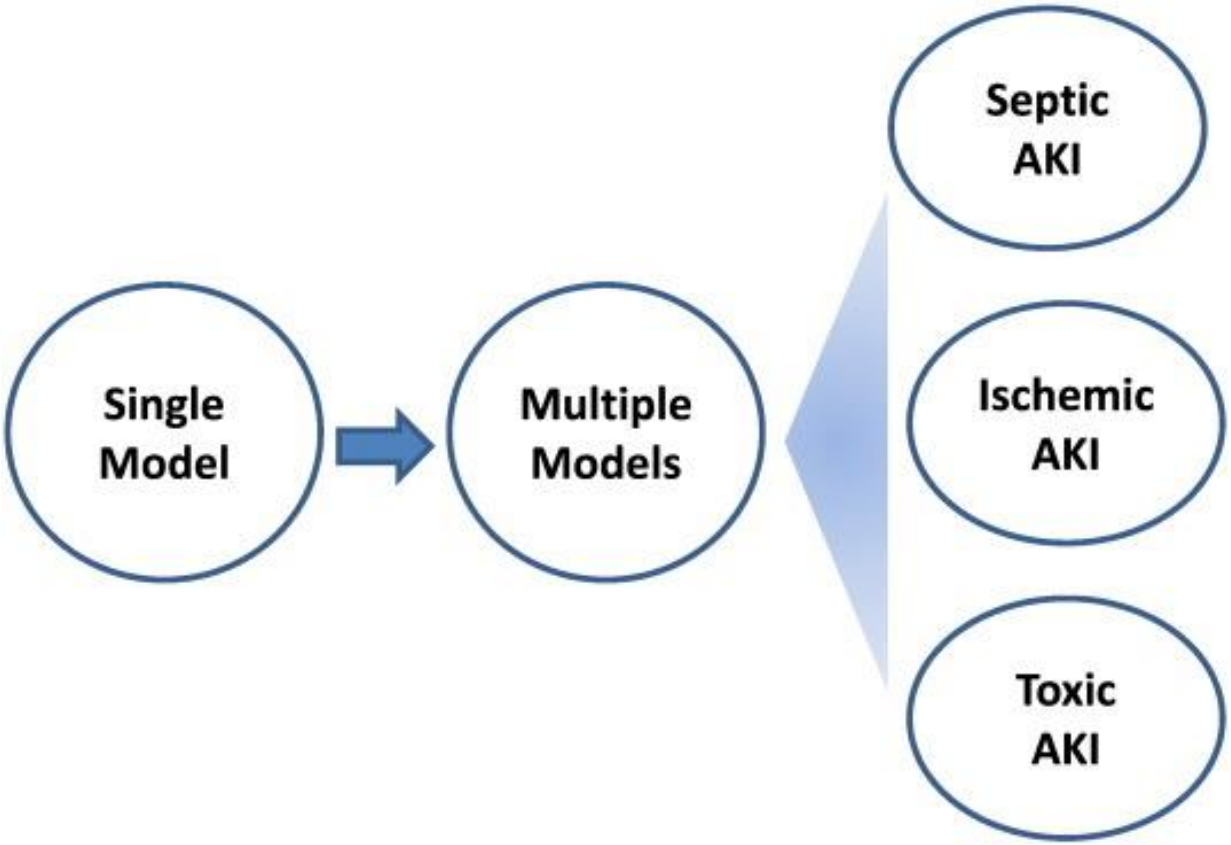


Experimental strategies for identifying renoprotective approaches for AKI: from rodent to mammalian models.



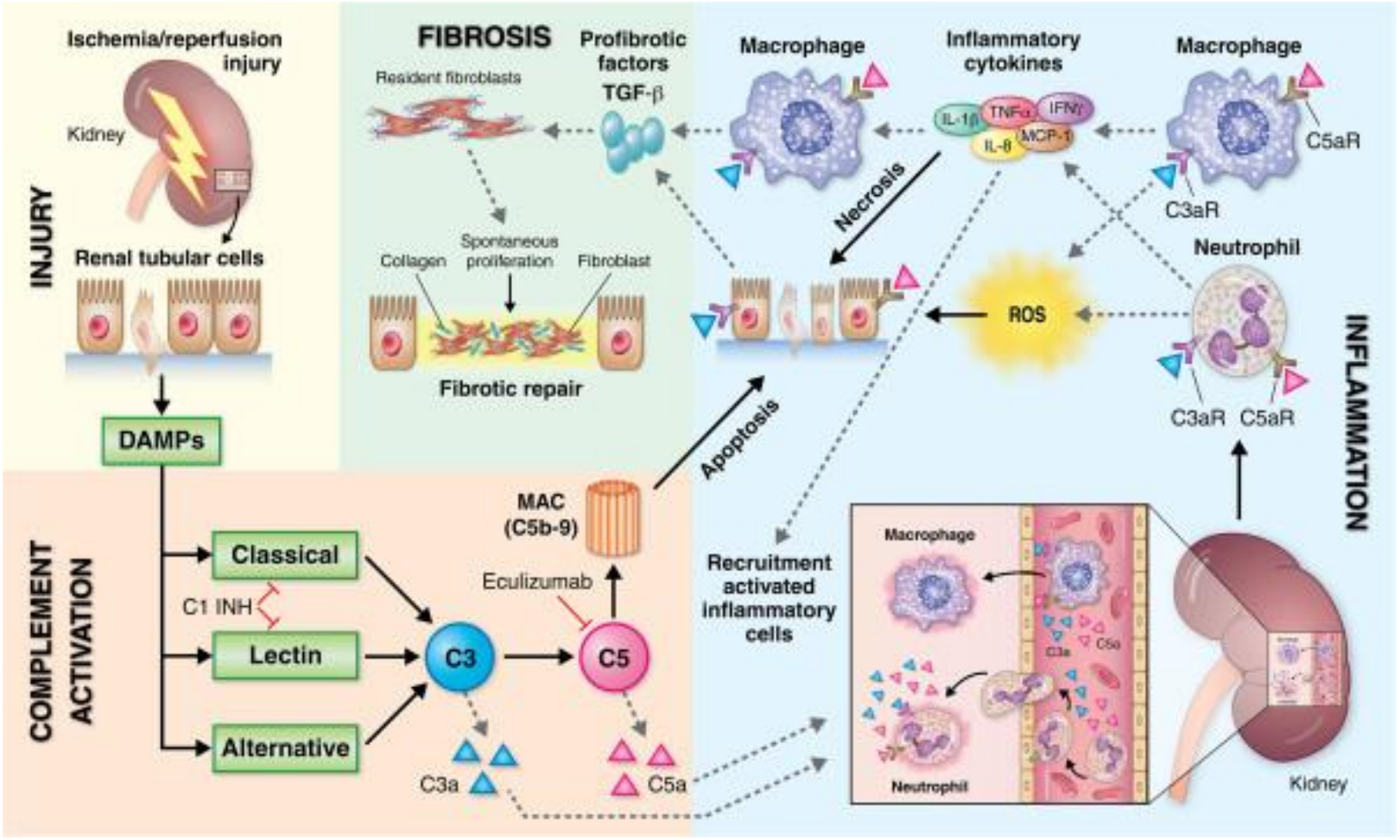
Zheng Dong 2016

Experimental strategies for identifying renoprotective approaches for AKI: from single to multiple models.



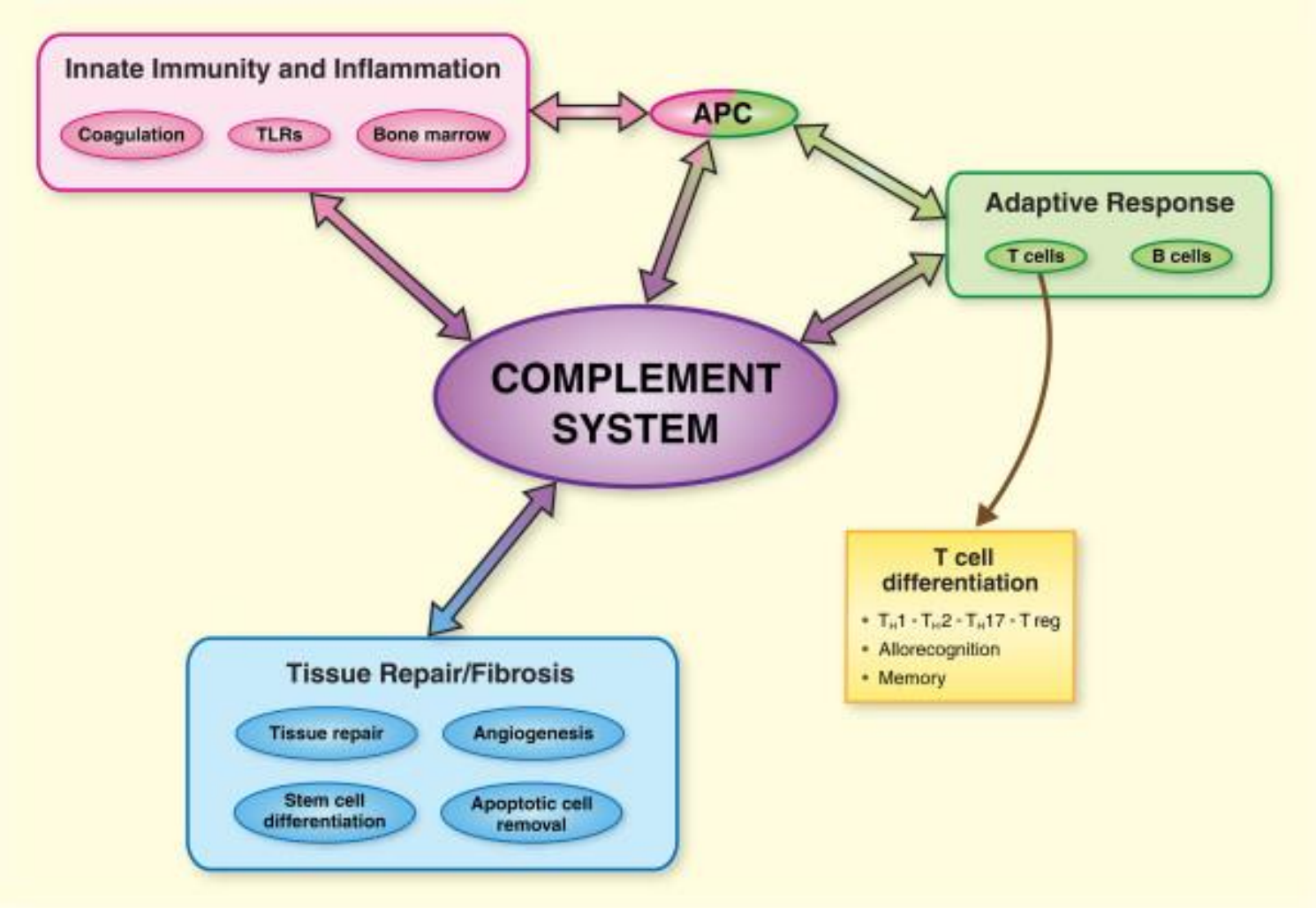
Zheng Dong 2016

Role of complement in renal ischemia-reperfusion injury, inflammation, and progression to kidney fibrosis.



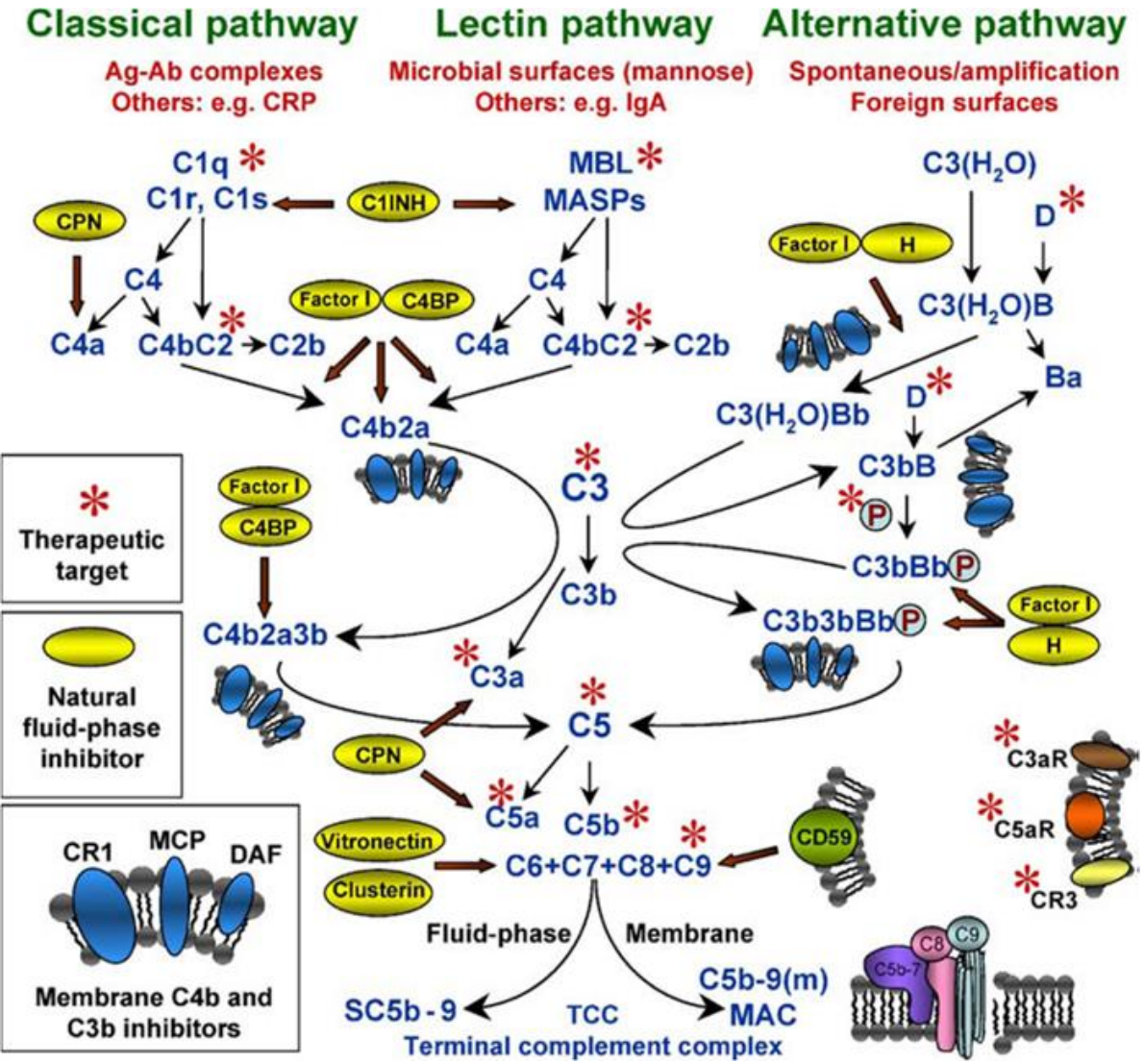
Fernandez 2014

Multifaceted activity of the complement system in immunity.



Fernandez 2014

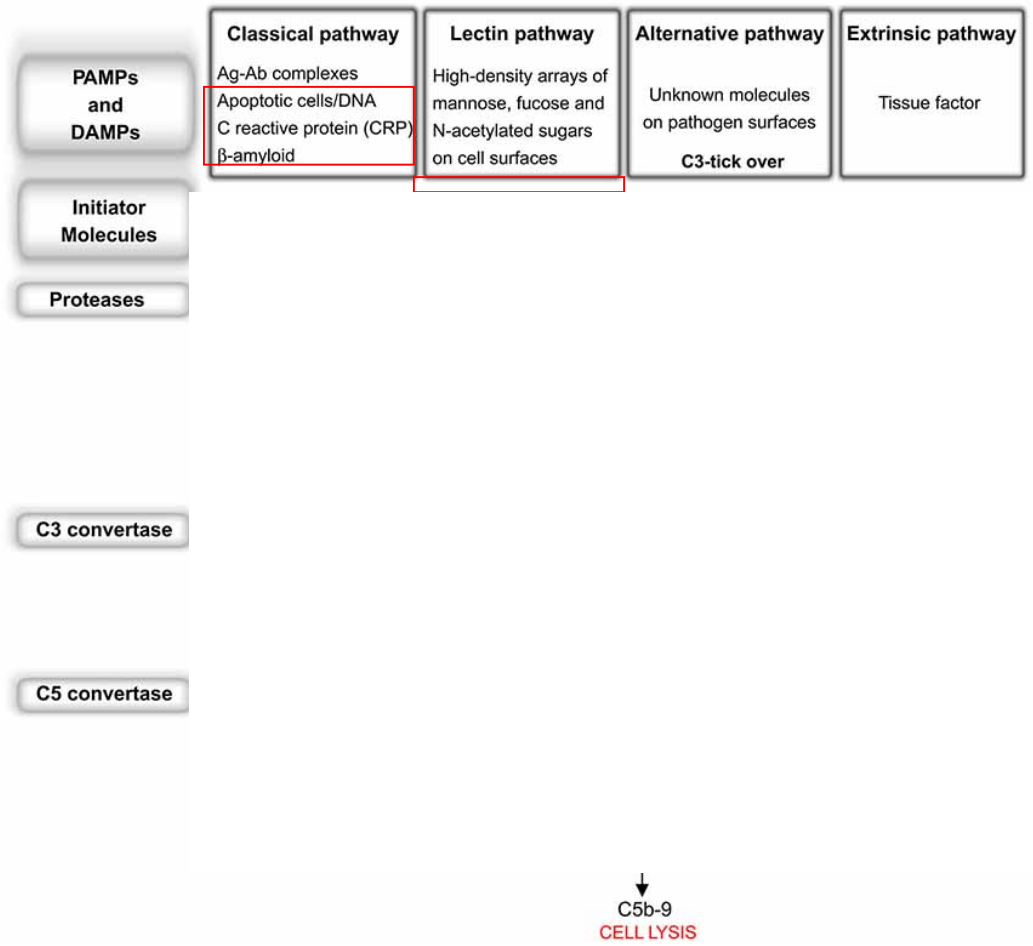
Complement System 1/2



- Complement system: a biochemical cascade made up of approximately 30 serum and membrane-bound proteins
- The primary location for biosynthesis of complement is the liver.
- The extrahepatic complement synthesis contributes **approximately 10% of circulating C3**. The alternative sites for complement production include epithelial cells, fibroblasts, lymphocytes and macrophages derived from different organs, including the **kidney.**

Nayareen Akhtar, American Journal of Medical Sciences,2014

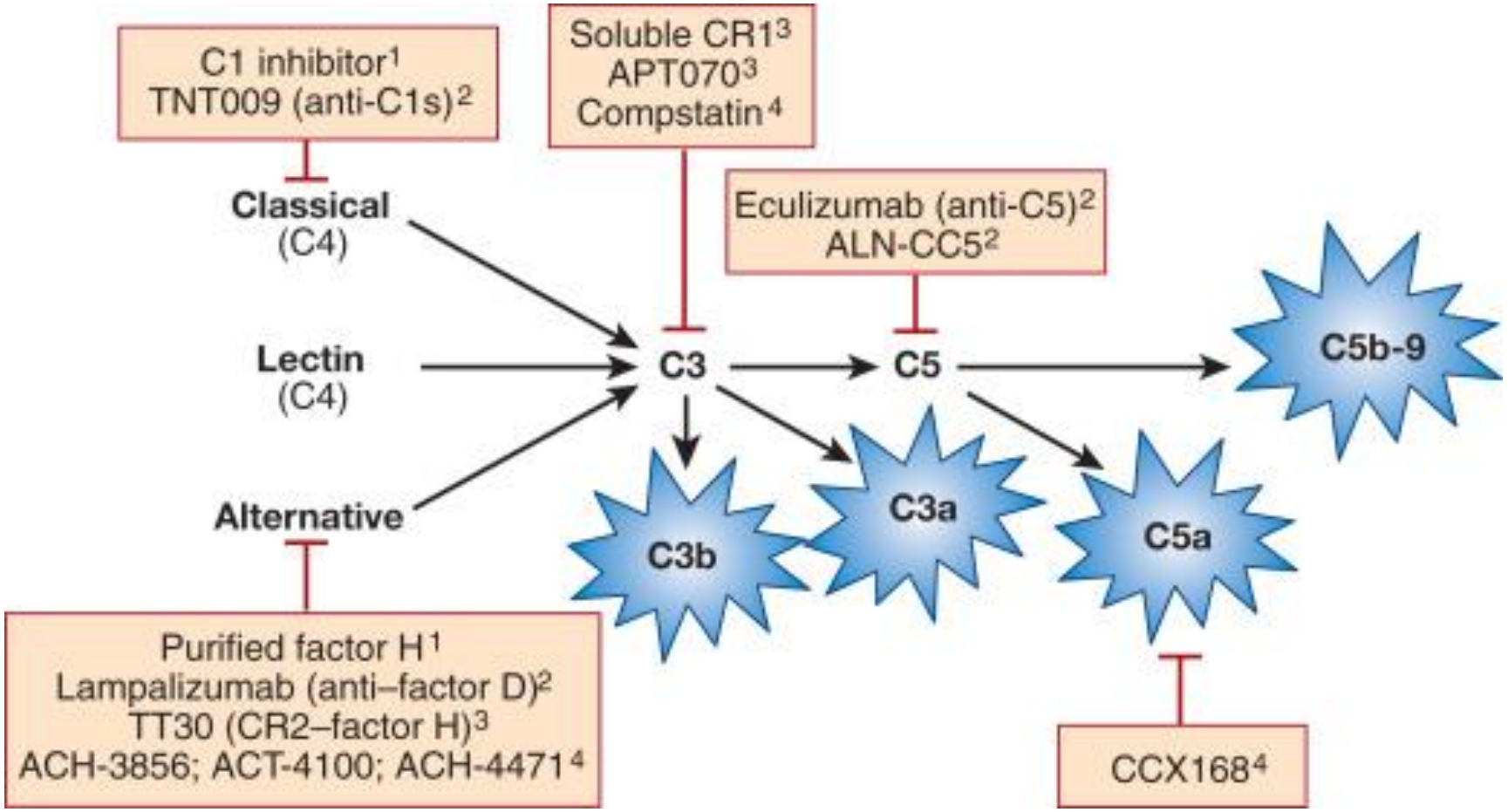
Complement System 2/2



- Complement activation initiates a cascade reaction, which leads to the cleavage of inert plasmatic components that generate bioactive components, including C3b, C3a, C5a, and C5b-9, with pro-inflammatory, chemo-attractant, and cell-damaging functions.

- A set of at least seven proteins in plasma (C1 INH, C4b-binding protein, factor H, and factor I) or cell membranes (decay-accelerating factor, membrane cofactor protein, and CR1 (CD35)) modulate the complement proteins and protect host cells and tissues from complement damage.

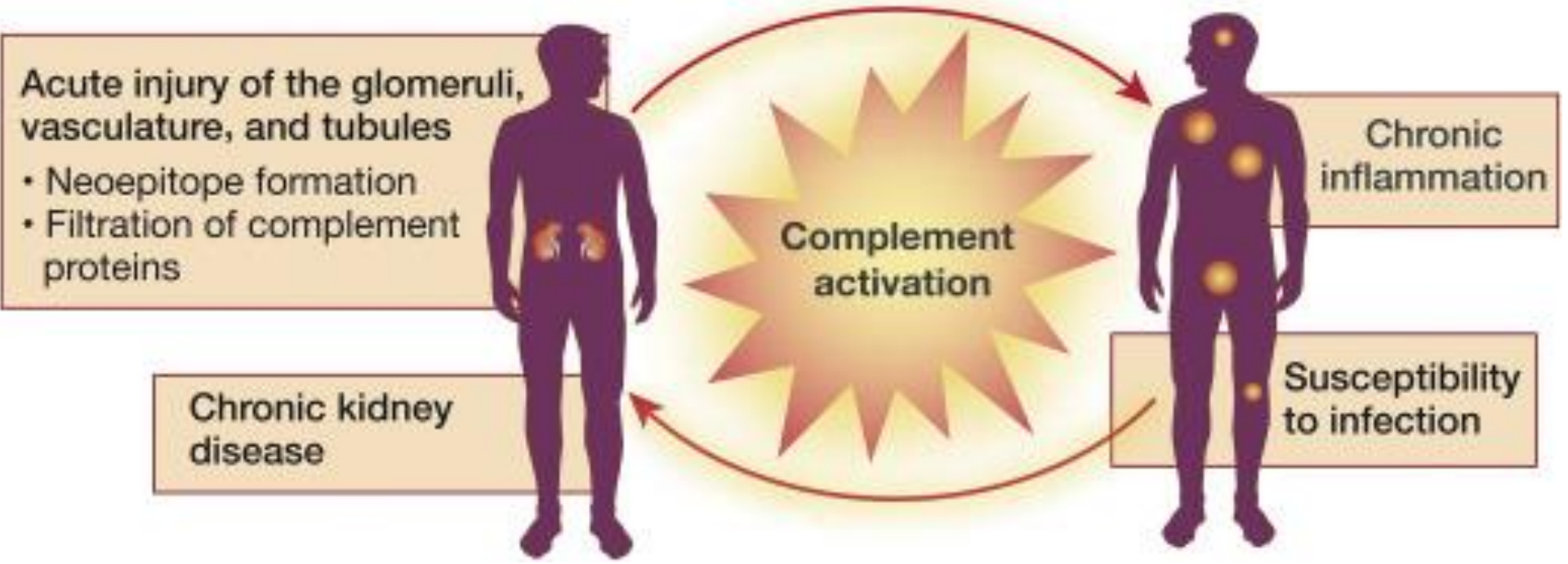
Targeting the complement cascade: novel treatments coming down the pike



Joshua M. Thurman, Moglie Le Quintrec

Kidney International, Volume 90, Issue 4, 2016, 746–752
http://dx.doi.org/10.1016/j.kint.2016.04.018

The complement system and kidney disease



Joshua M. Thurman, Moglie Le Quintrec

Targeting the complement cascade: novel treatments coming down the pike

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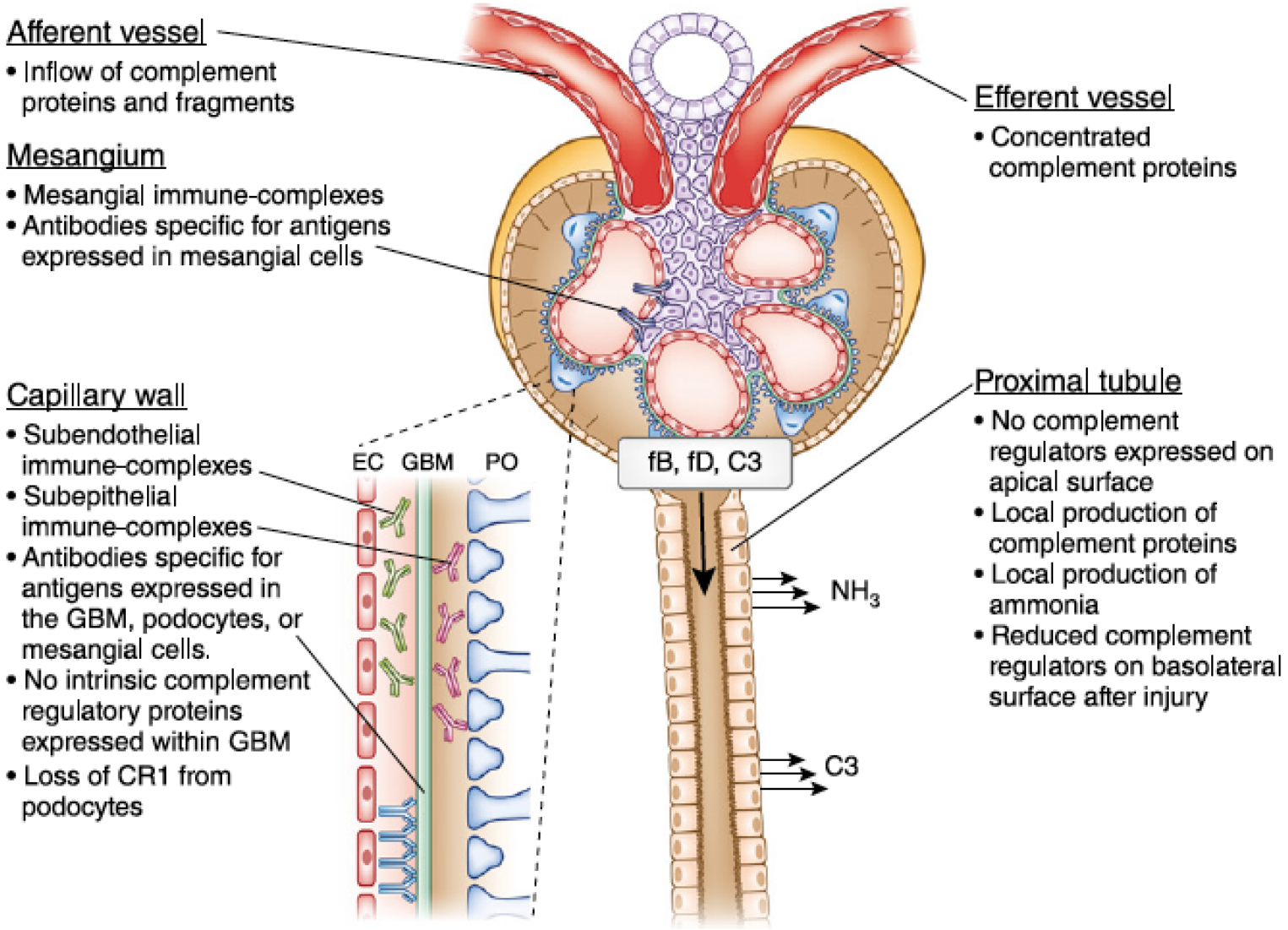
The complement system and kidney disease



Local Renal Synthesis of Complement

JCI

Interleukin 2 mediates stimulation of complement C3 biosynthesis in human proximal tubular epithelial cells.

R A Brooimans, A P Stegmann, W T van Dorp, A A van der Ark, F J van der Woude, L A van Es, and M R Daha

The first study to demonstrate that human renal proximal tubular epithelial cells synthesised and secreted complement component C3 in vitro was published by Brooimans et al. more than 20 years ago.

Resident renal cells, including tubular and glomerular epithelial cells, mesangial cells and endothelial cells can synthesise many, if not all complement proteins

British Society for immunology

Complement C3 gene expression and regulation in human glomerular epithelial cells.

S H Sacks, W Zhou, A Pani, R D Campbell, and J Martin

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ELSEVIER

Kidney International

Volume 51, Issue 3, March 1997, Pages 703-710

kidney

Laboratory Investigation

TNF-α regulation of C3 gene expression and protein biosynthesis in rat glomerular endothelial cells

Neil S. Sheerin, Wuoing Zhou, Stephen Adler, Steven H. Sacks

Transforming growth factor-β1 regulates chemokine and complement production by human proximal tubular epithelial cells

Jort S.J. Gerritsma, Cees van Kooten, Arnout F. Gerritsen, Leendert A. van Es, Mohamed R. Daha

Intrarenal local complement synthesis is an important mediator in disease progression

Pediatric RESEARCH

0013

Evidence of a Role for Local Complement Expression in a Murine Model of Progressive Glomerulonephritis

Thomas R Welch[1,3], Marie Frenzke[1,3] and David Witte[2,4]

Local Synthesis of Complement System induces Acute Rejection (1)

ARTICLES

Local synthesis of complement component C3 regulates acute renal transplant rejection

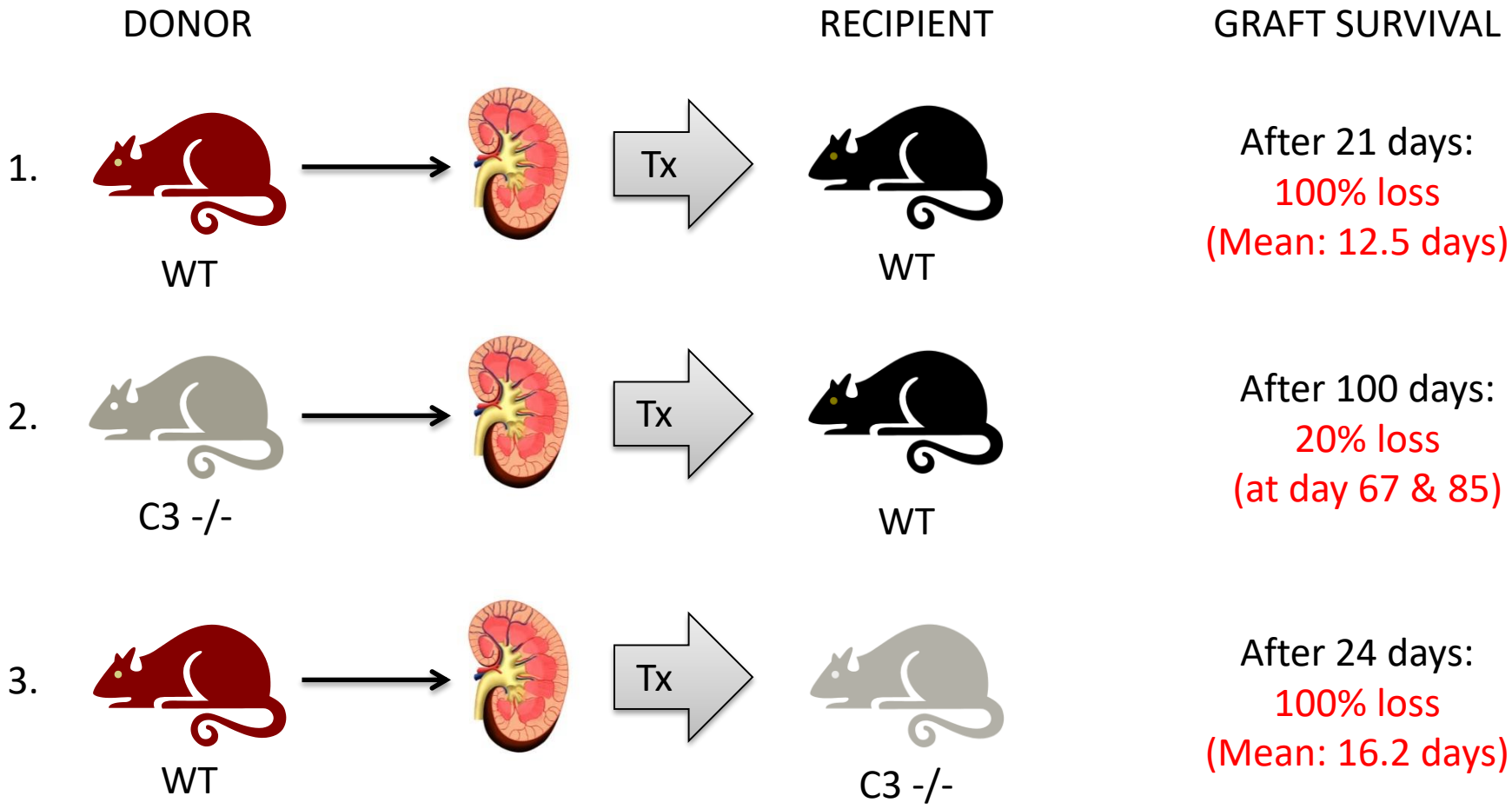
JULIAN R. PRATT, SHAMIM A. BASHEER & STEVEN H. SACKS

Department of Nephrology & Transplantation, King's College University of London, Guy's Hospital, London, UK
Correspondence should be addressed to S.H.S.; email: steven.sacks@kcl.ac.uk

NATURE MEDICINE • VOLUME 8 • NUMBER 6 • JUNE 2002

Local Synthesis of Complement System induces Acute Rejection (2)

Experimental Design:



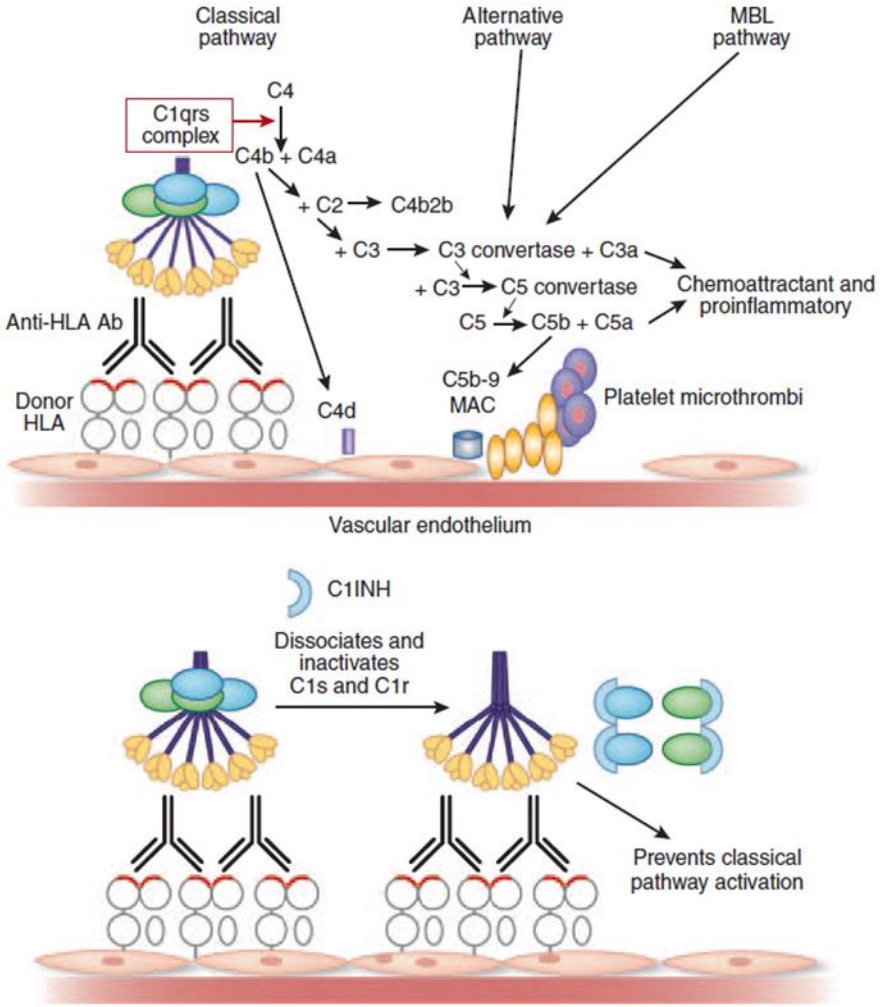
Clinical use of Complement inhibitors

- ✓ Currently, there are 2 FDA approved drugs aimed at inhibition of complement activation:

- ✓ Eculizumab (anti-C5) which is approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

- ✓ C1-Inhibitor (C1-INH), which is approved for use in patients with hereditary angioedema

C1 – INH as Complement system inhibitor in Kidney transplantation



Peter S. Heeger. Kidney international 2010

One of the cardinal features of AMR is C4d (a fragment of C4 which remains on the target after C activation). C1-INH inactivates both C1r and C1s and is the only plasma protease that regulates the classic complement pathway thus preventing proteolytic activation of C4 and C2 that form C3 convertase

C1-INH can also inhibit the analogous serine proteases in the lectin pathway of C activation, as well as the alternative pathway through regulation of factor B binding to C3b as well as factor B cleavage by factor D

C1-INH also has major effects on activation of the coagulation cascade and on regulation of vascular permeability and inflammation by kinins

Complement in immune-mediated renal disease

1. **Brain death /Cardiac Arrest**
2. **Ischemia/Reperfusion Injury**
3. **Lupus Nephritis**
4. **IgAN**
4. **aHUS**

The pathophysiology of brain death

Brain Death
Cerebral injury and edema
Brain stem herniation

↓

Immunological activation
Cytokine storm
Systemic inflammation
Complement activation

↓

Tissue injury
Apoptosis/necrosis

↓

Reduced organ viabilty
Allo-response
Delayed graft function

Brain death (BD) is complex and causes a **systemic** and **local inflammatory response** and resembles the systemic inflammatory response syndrome (**SIRS**).

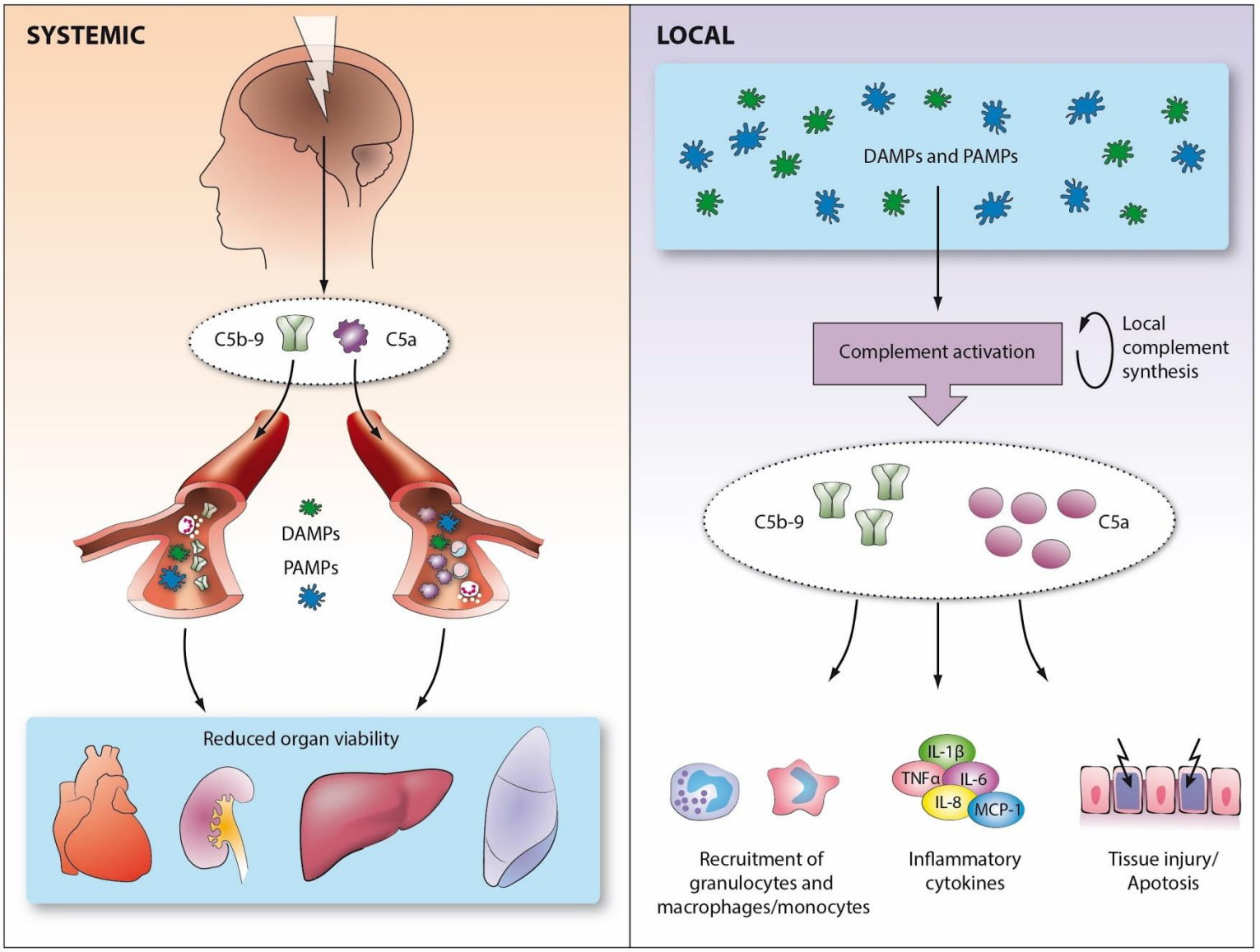
The cause of this immune activation is not well understood.

Kidney from brain-dead organ donors give inferior results results compared to kidneys from living donors:

Organ transplanted	1-year survival		5-year survival	
	2001–2002	2002–2003	1997–2002	1998–2003
Kidney				
Living donor	94.3%	94.6%	78.6%	79.2%
Deceased donor	88.7%	89.0%	65.7%	66.2%

Source: UNOS/OPTN.

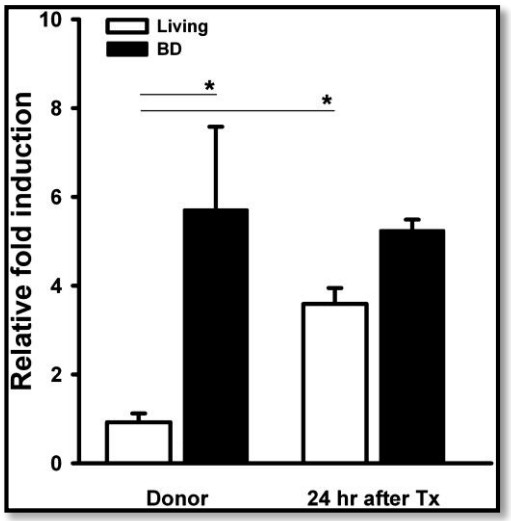
The complement system in brain death



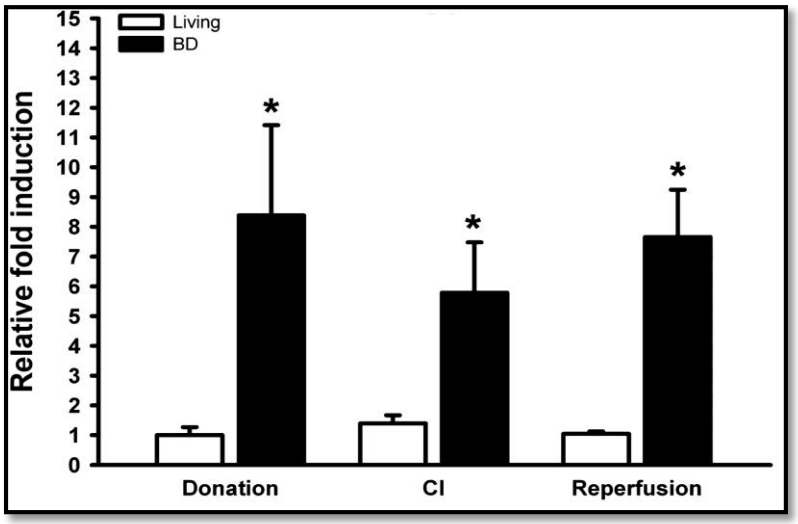
Poppelaars F, et al. Complement-mediated inflammation and injury in brain dead organ donors. Unpublished data.

Local complement production by the kidney

Renal C3 expression in rats



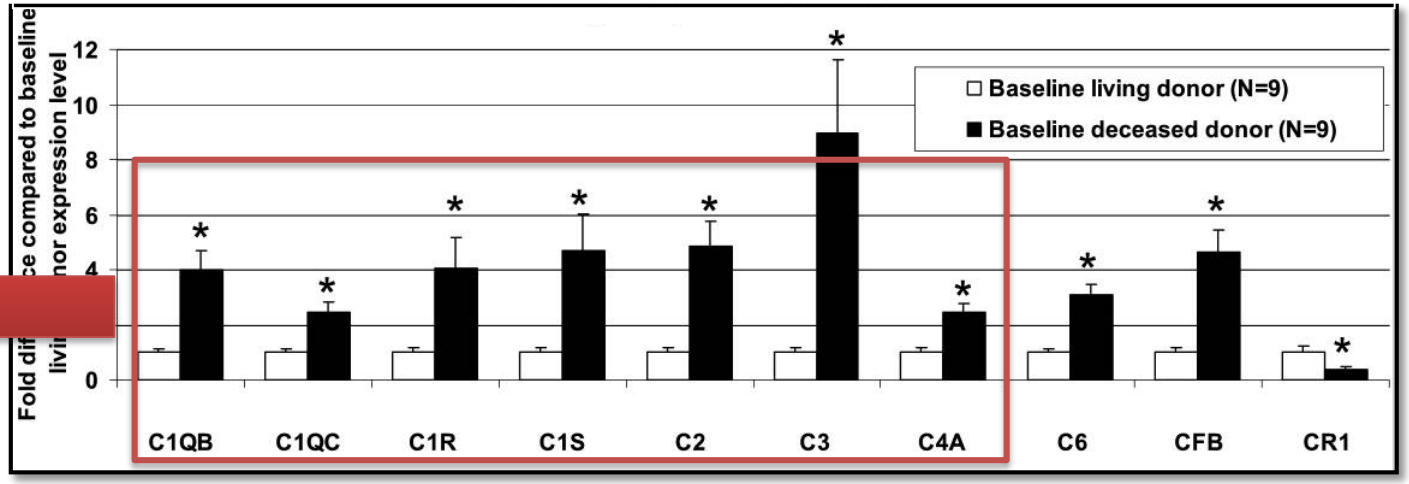
Renal C3 expression in humans



Jeffrey Damman, et al. *Nephrol Dial Transplant.* 2011 Jul;26(7):2345-54.

Renal expression of complement in the donor graft

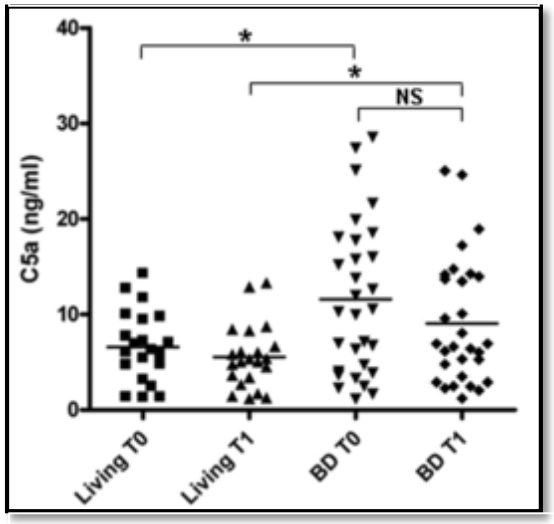
Components of the CP



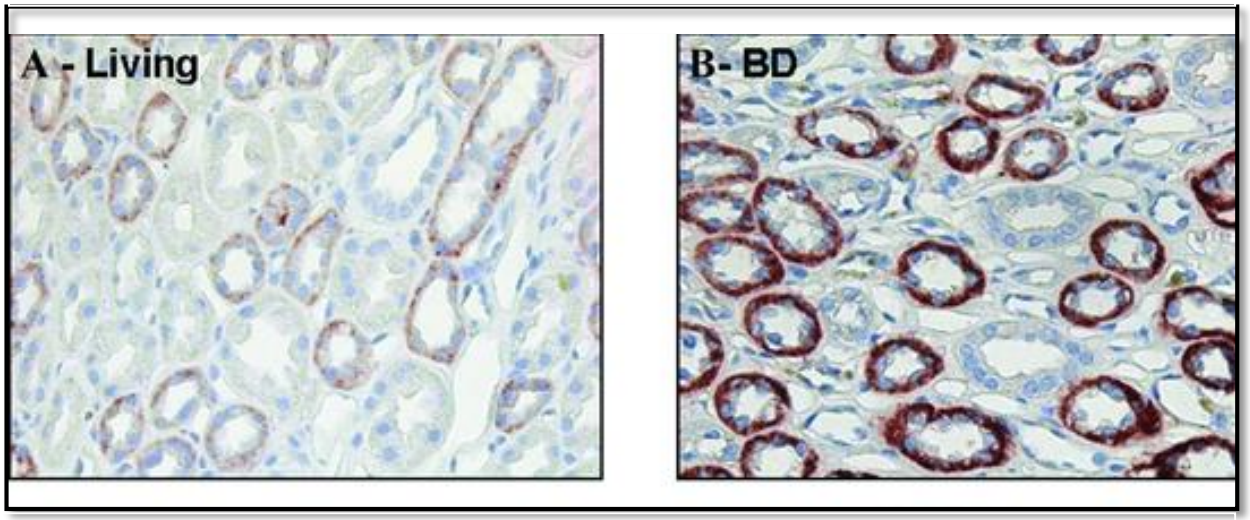
Maarten Naesens, et al. *J Am Soc Nephrol*. 2009 Aug; 20(8):1839-51.

The role of C5a in brain-dead donors

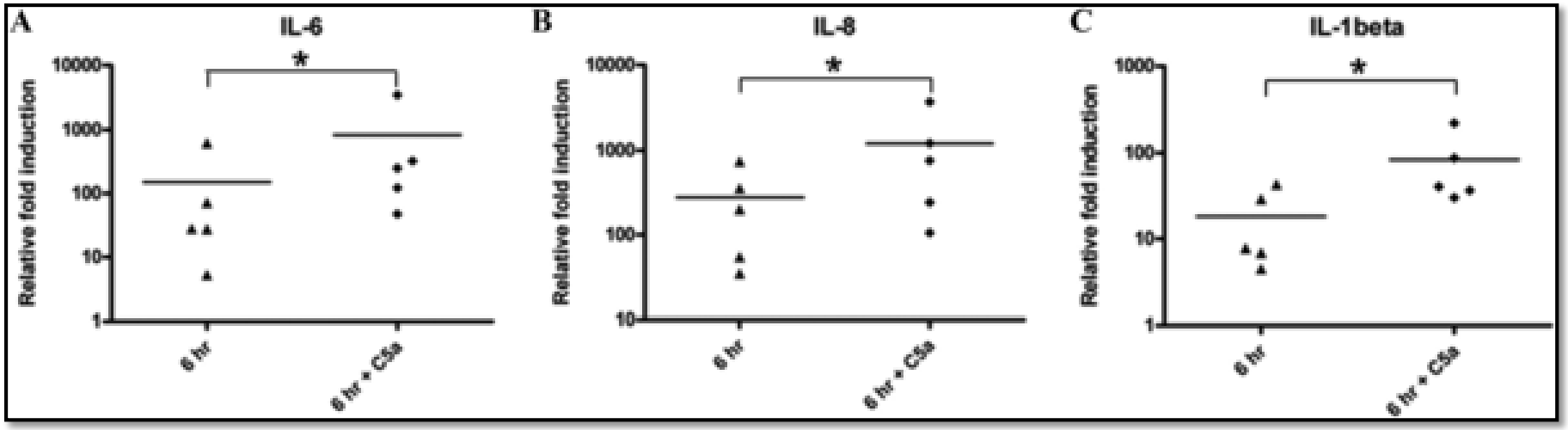
Plasma C5a levels



Renal C5a-Receptor expression



The effect of renal C5a-C5aReceptor activation



Maaike van Werkhoven, et al. *Am J Transplant.* 2013 Apr;13(4):875-82.

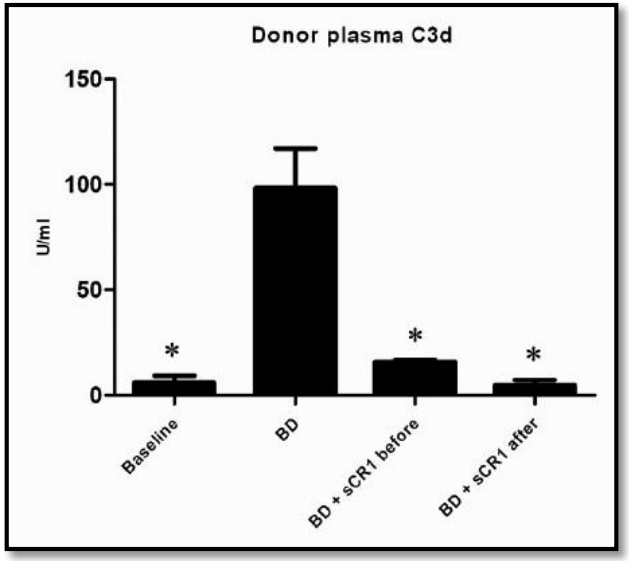
Complement inhibition in brain-dead donors

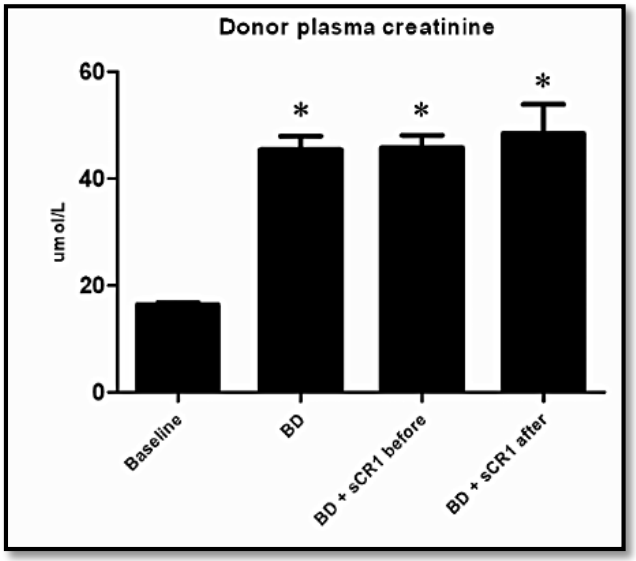
Animal model:
Rat Brain death with Renal transplantation.

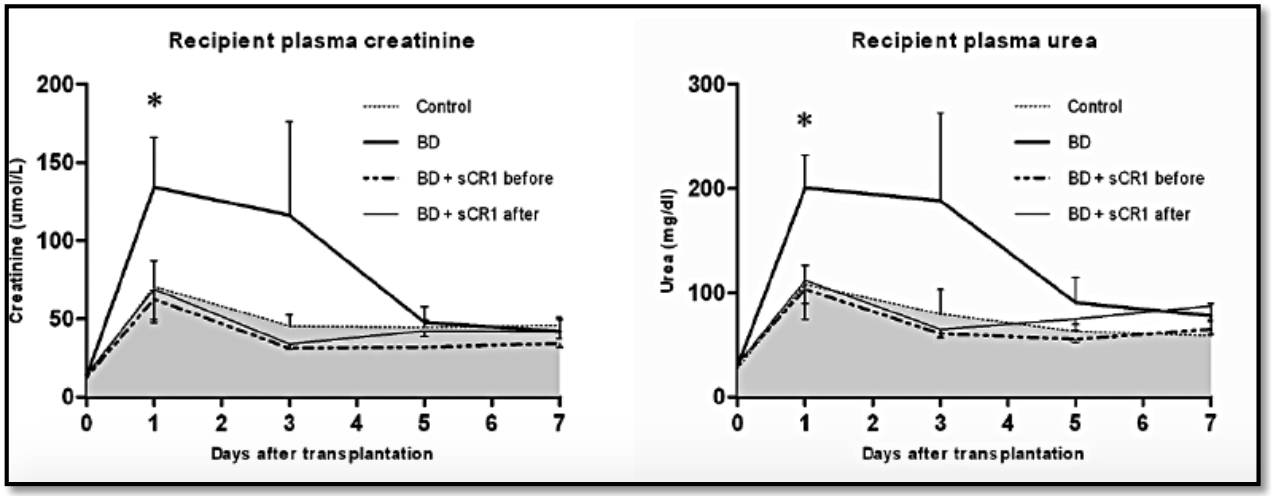
Intervention:
sCR1 = C3 inhibitor (soluble Complement Receptor 1)

Treatment:
- Before BD induction
- After BD induction

Conclusion:
Complement inhibition improves renal function after Tx in the recipient.

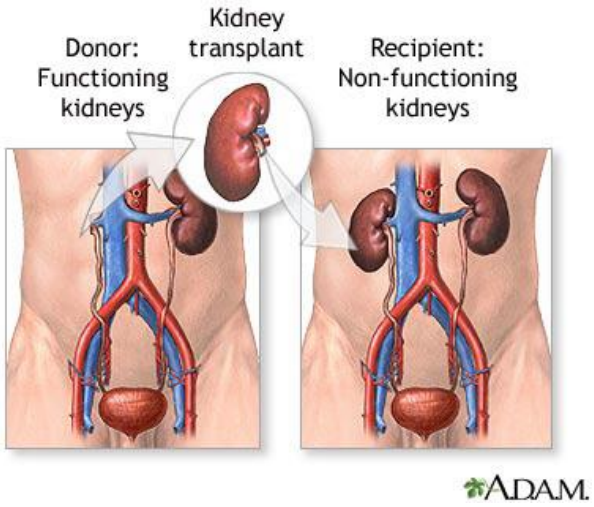




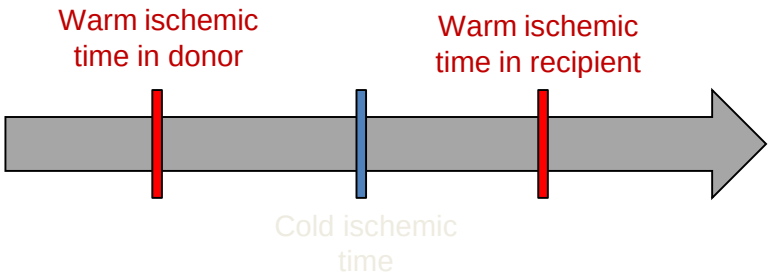


Jeffrey Damman, et al. *Transpl Immunol.* 2011 May;24(4):233-7.

Ischemia/Reperfusion injury (IRI) in kidney transplantation

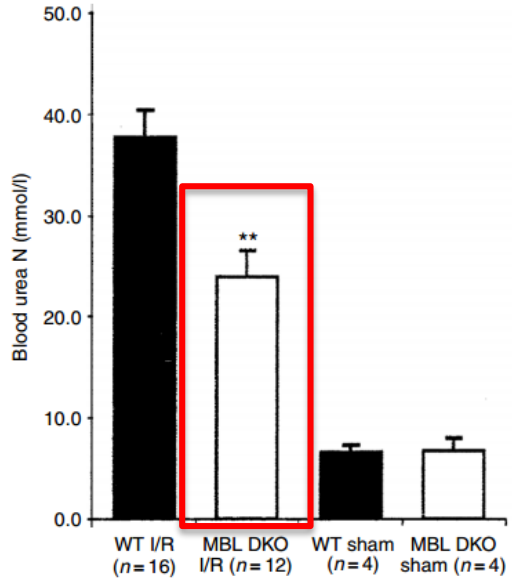


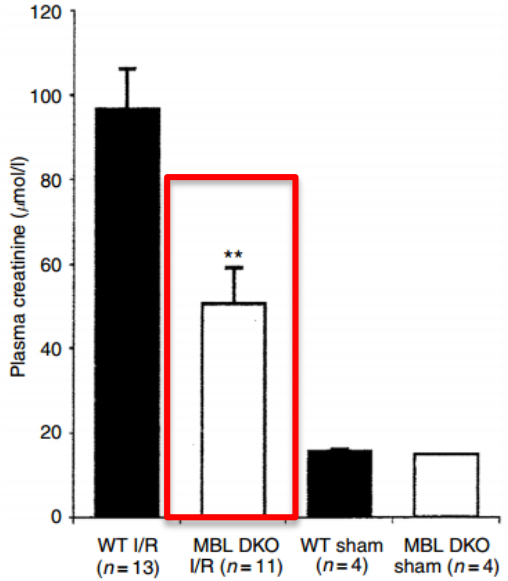
Renal Allograft	
Warm Ischemia Time (WIT)—time from extubation and cessation of circulation to removal of organ and perfusion with cold preservation solution	≤ 60 minutes
Cold Ischemia Time (CIT)—time from initiation of cold preservation solution to restoration of warm circulation after transplantation.	≤ 72 hours (≤24 hours ideal)



IRI is a frequent event in kidney transplantation, particularly when the kidney comes from a deceased donor, and can heavily influence both the early and the late function of a kidney allograft

The Lectin Pathway in IRI





•The recognition molecules of the MBL pathway include mannose binding lectins or ficolins.
These molecules bind to carbohydrate motifs displayed on the surface of bacteria, but MBL could bind neo-epitopes that are generated or exposed within the injured kidney (i.e Cytokeratin)

•*Patients with high circulating concentrations of MBL have a poor outcome after renal transplantation*.

Berger SP, AJP 2005

•**Animal model**

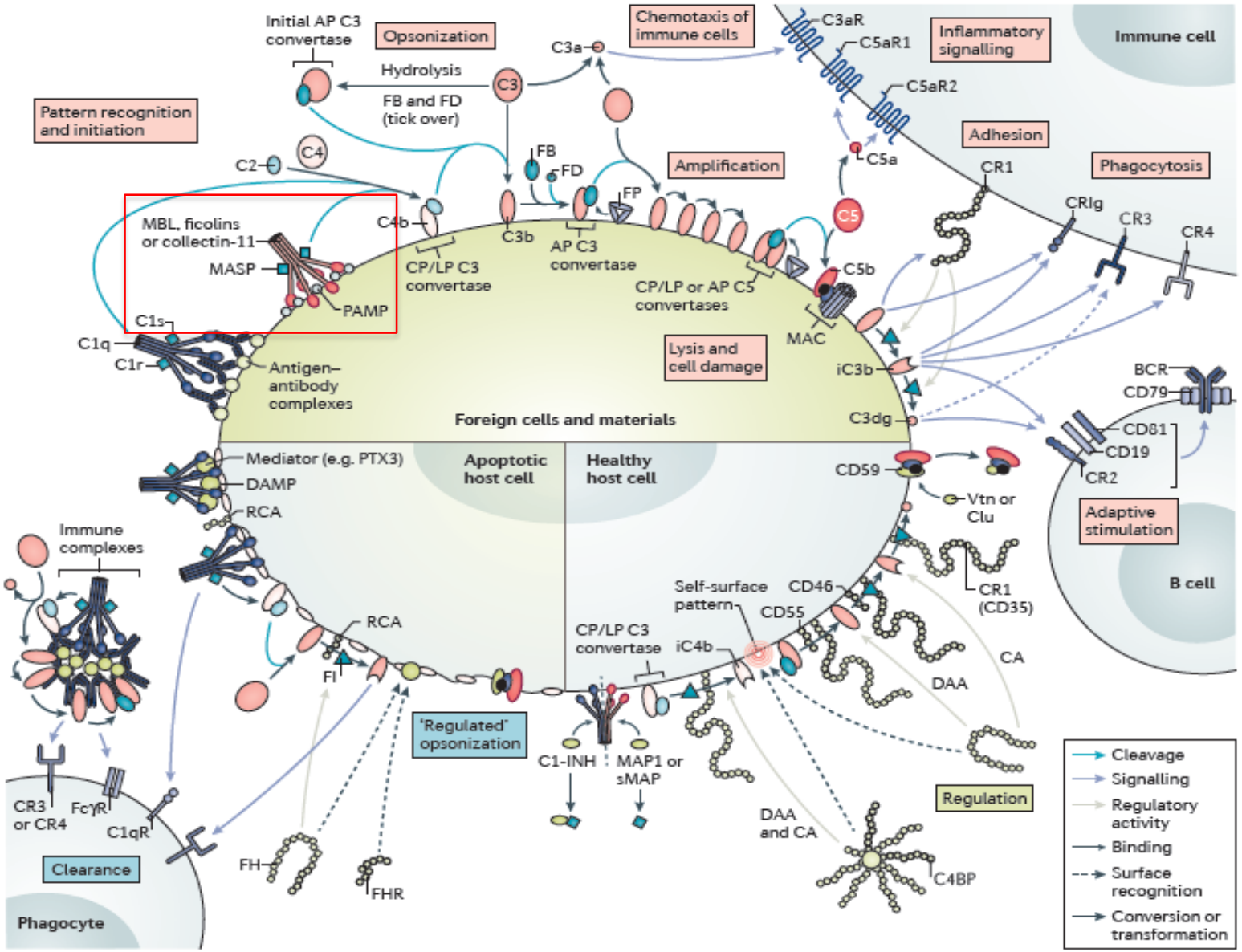
Transgenic mice deficient in both MBL-A and MBL- C, renal I/R injury

•**Results**

-Level of BUN and Creatinine showed that MBL double knouck-out mice were protected by IRI, compared to WT mice.

-The protective phenotype was reversed following reconstitution of the mutant mice with recombinant MBL .

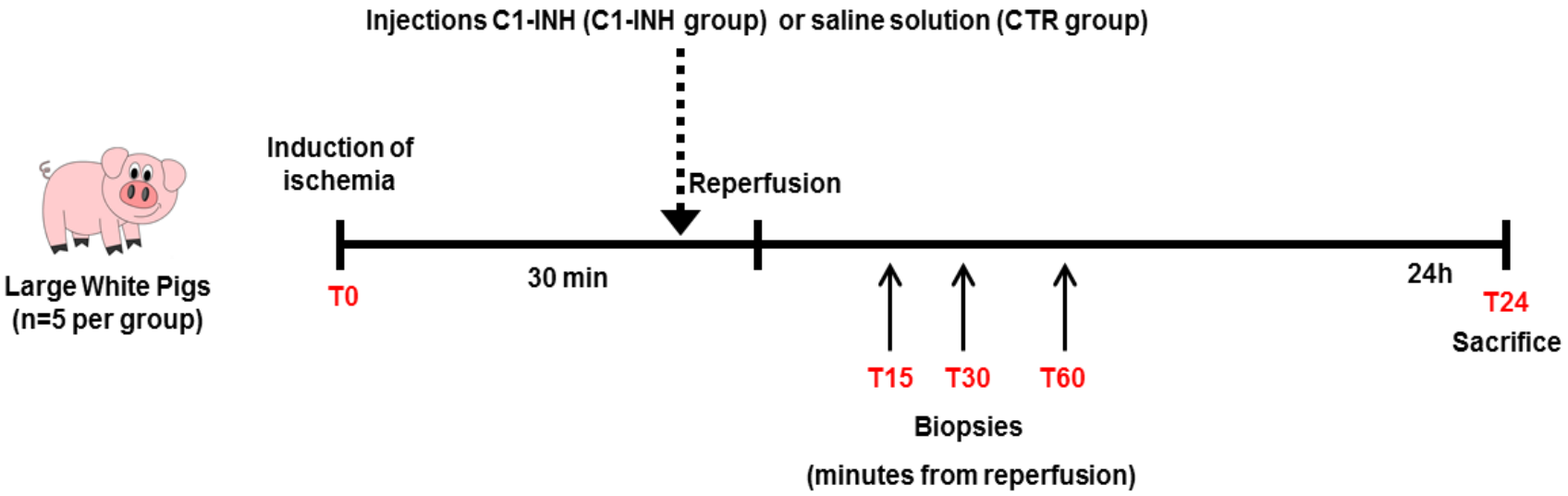
Moller-Kristensen et al., 2005



Ricklin D, Nat Rev 2016

Swine model of IRI

Recombinant Human C1- INH
(Ruconest, Pharming, Leiden, The Netherlands)

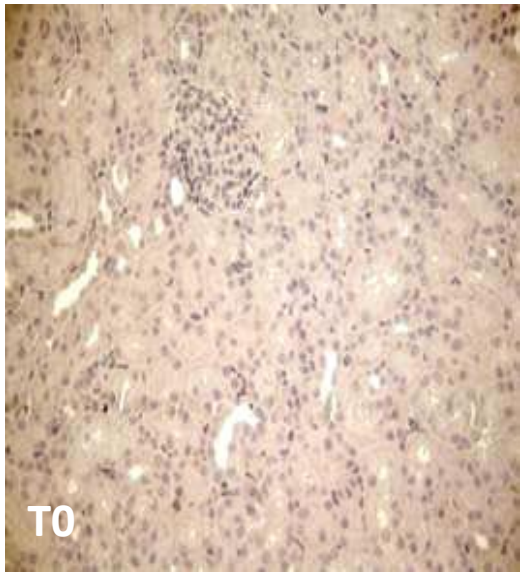


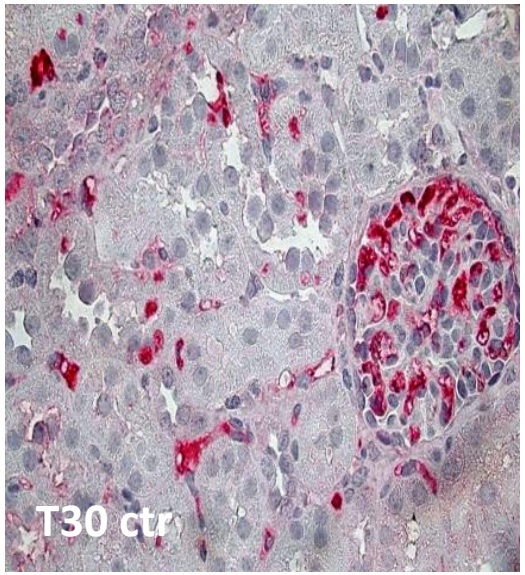
Am J Pathol. 2010 Apr;176(4):1648-59. doi: 10.2353/ajpath.2010.090276. Epub 2010 Feb 11.

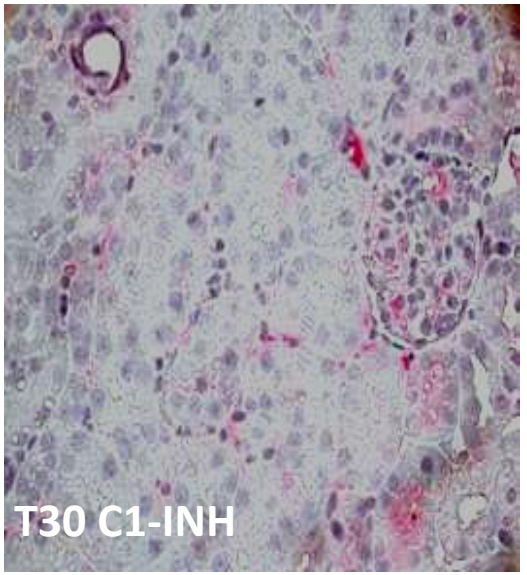
Therapeutic targeting of classical and lectin pathways of complement protects from ischemia-reperfusion-induced renal damage.

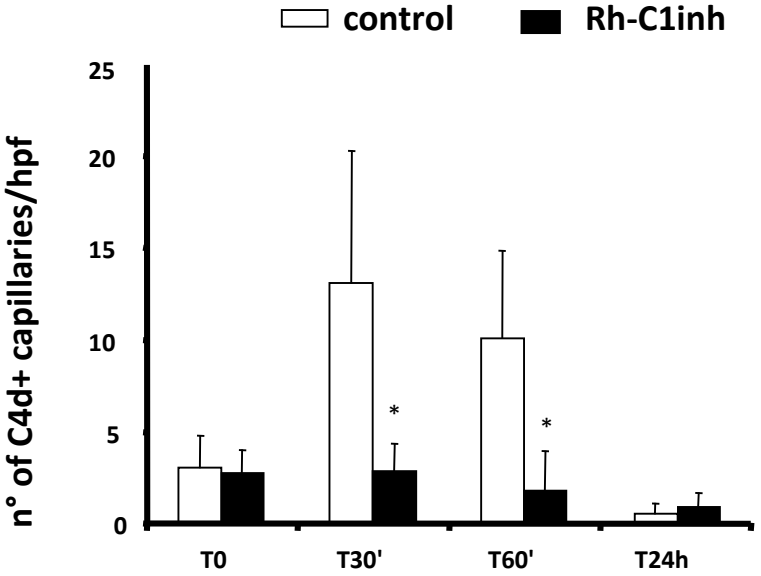
Castellano G[1], Melchiorre R, Loverre A, Ditonno P, Montinaro V, Rossini M, Divella C, Battaglia M, Lucarelli G, Annunziata G, Palazzo S, Selvaggi FP, Staffieri F, Crovace A, Daha MR, Mannesse M, van Wetering S, Paolo Schena F, Grandaliano G.

C1-INH inhibits C4d deposition



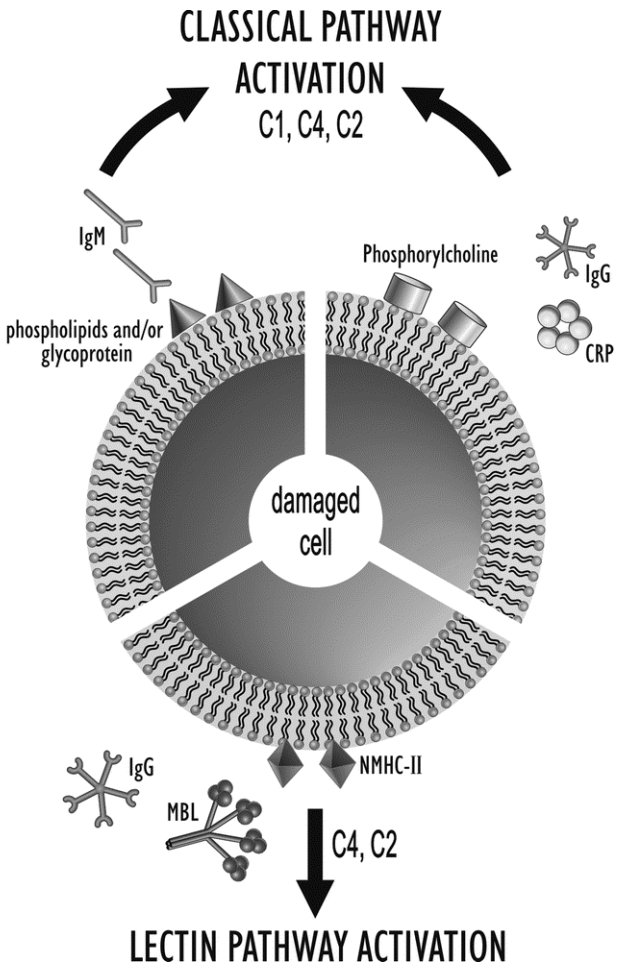




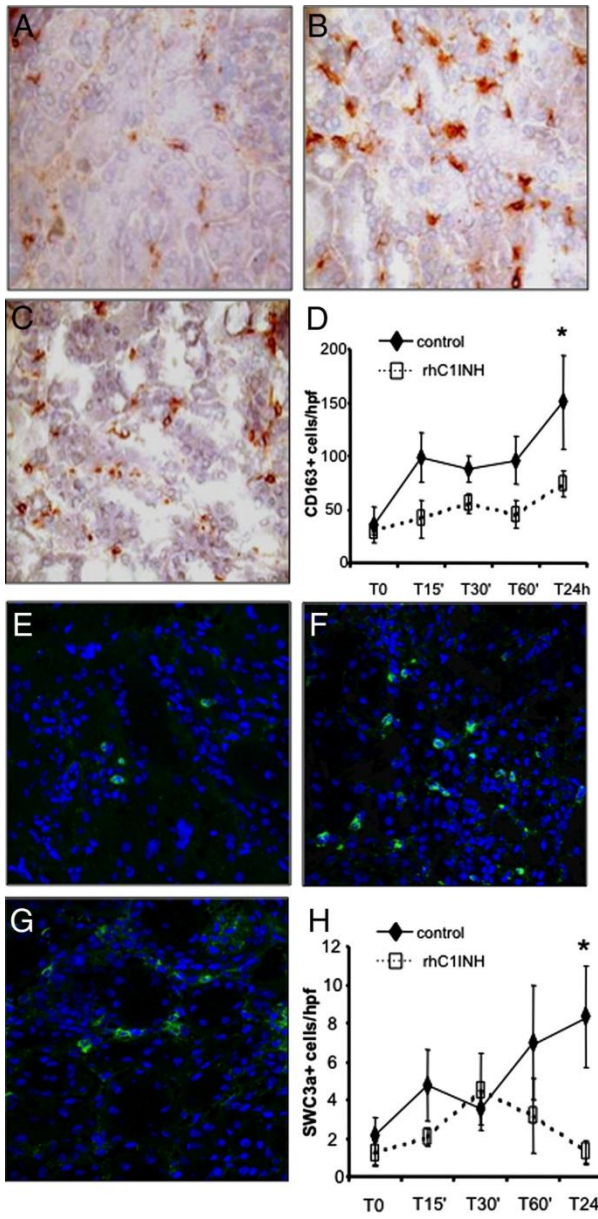


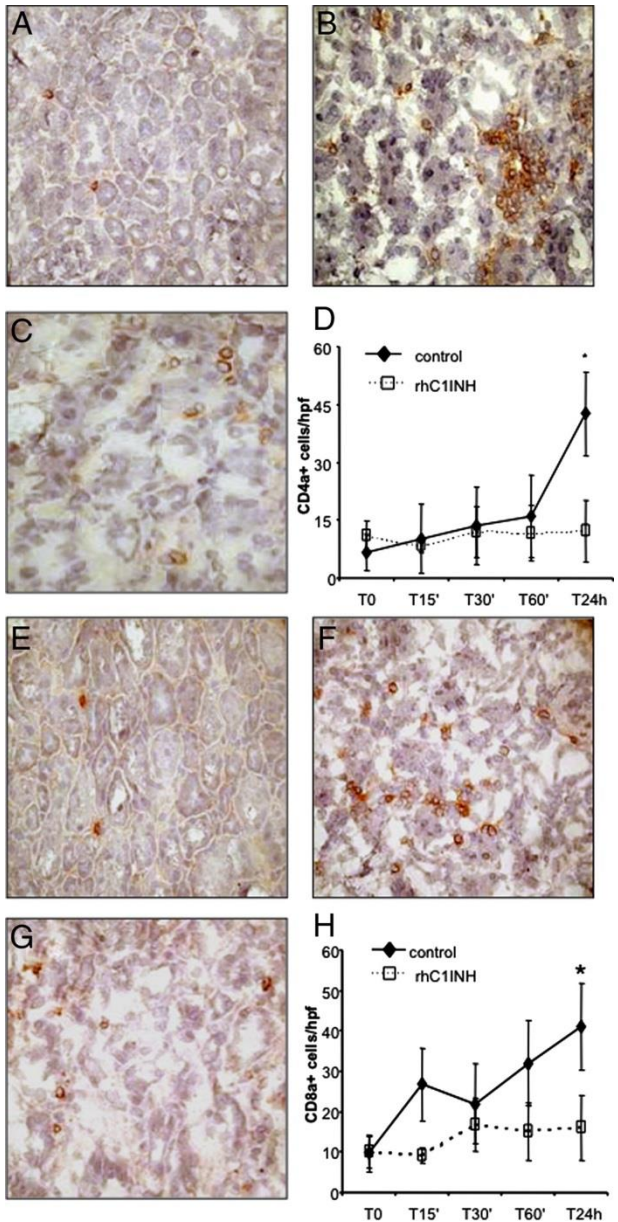
Castellano et al, Am J Pathol, 2010

C4d deposits on renal Endothelial Cells

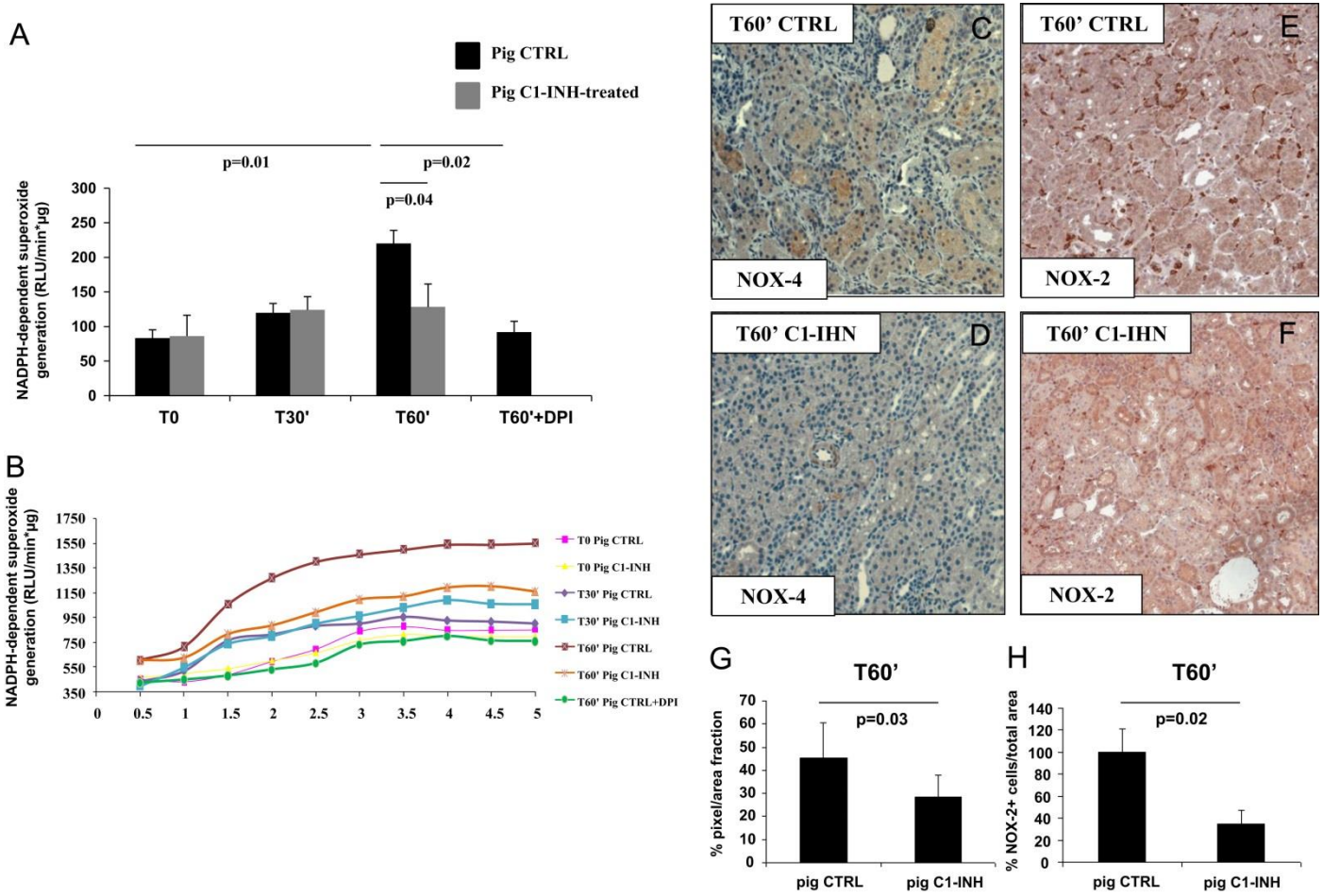


C1-INH treatment significantly reduced the numbers of inflammatory infiltrating cells





C1-INH infusion modulates NADPH activity and NOX-4 and NOX-2 expression

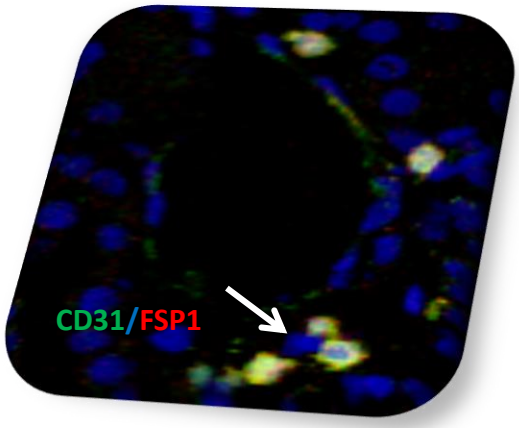


Simone S et al. Free Radic Biol Med, 2014

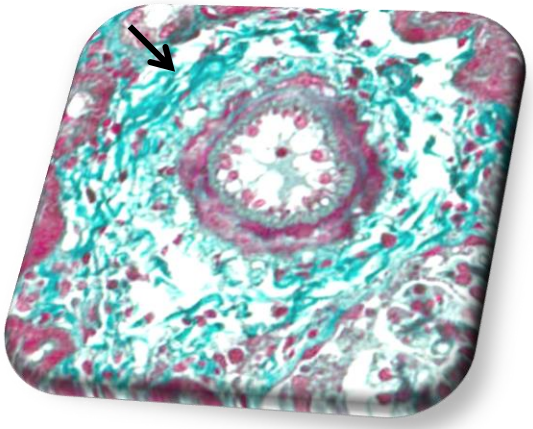
Complement-mediated endothelial dysfunction in I/R injury

In vivo

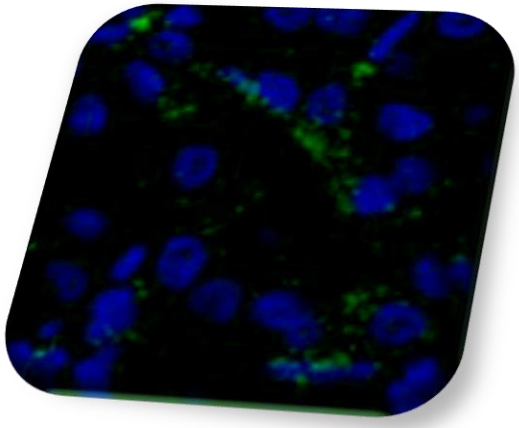
T24h ctr



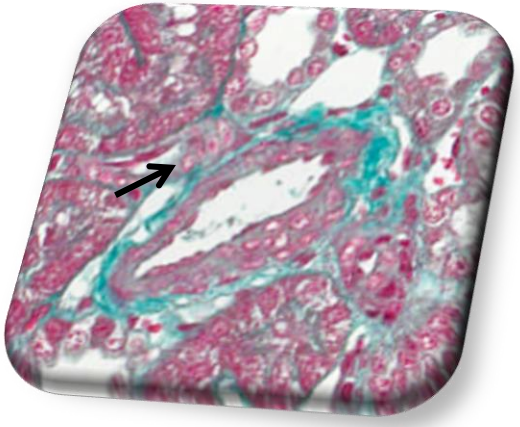
T24h ctr



T24h C1-INH

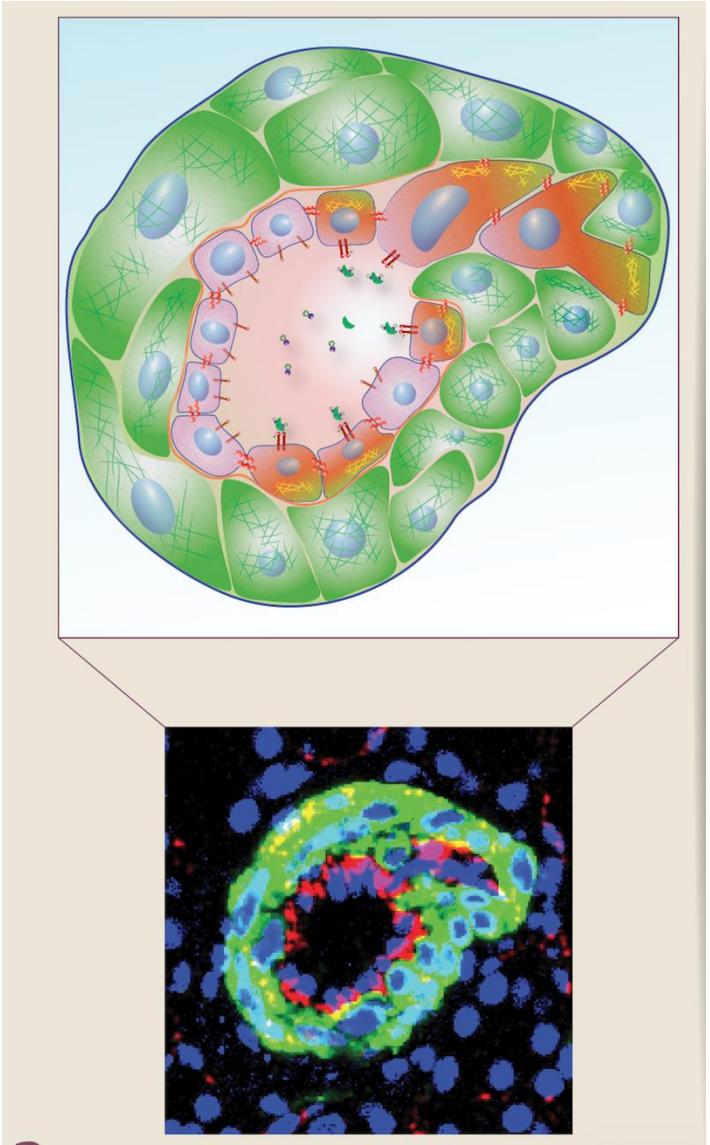


T24h C1-INH



Curci C.,Castellano G. Nephrol Dial Transplant. 2014

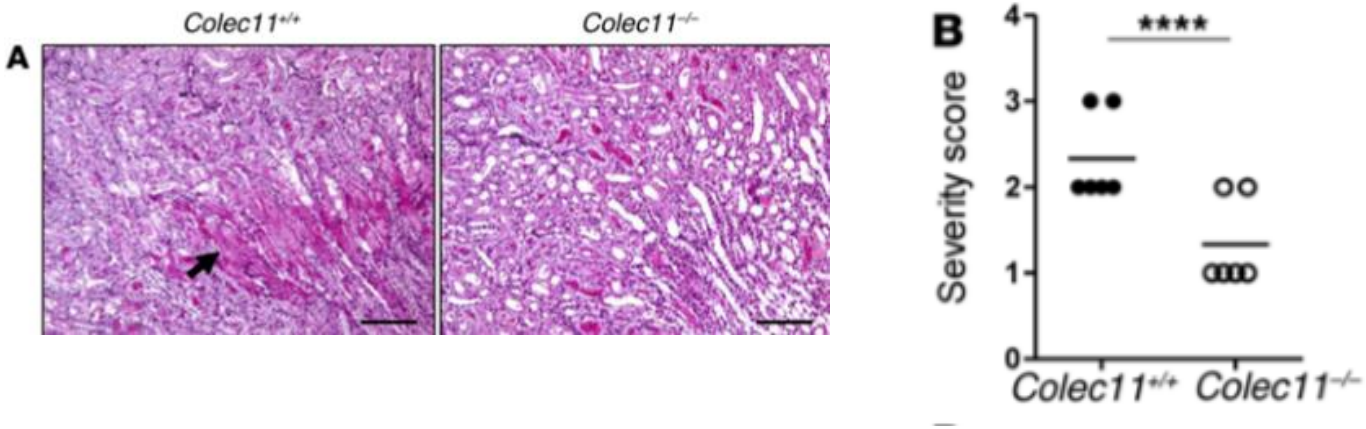
Endothelial to Mesenchimal Transition in AKI



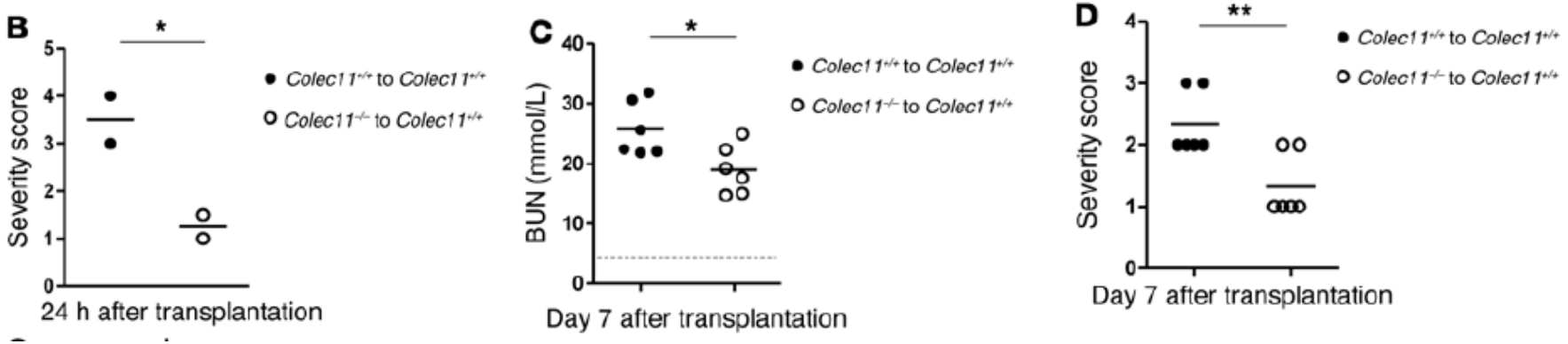
Stasi et al, NDT 2016

Emerging role of Colec11 in IRI

IRI : Absence of CL-11 in *Colec11–/–* mice permitted a less severe loss of renal function, with good preservation of renal architecture (Fig A, PAS staining) reduced leukocyte infiltration and tubular deposition of complement compared with that seen in *Colec11+/+ mice*

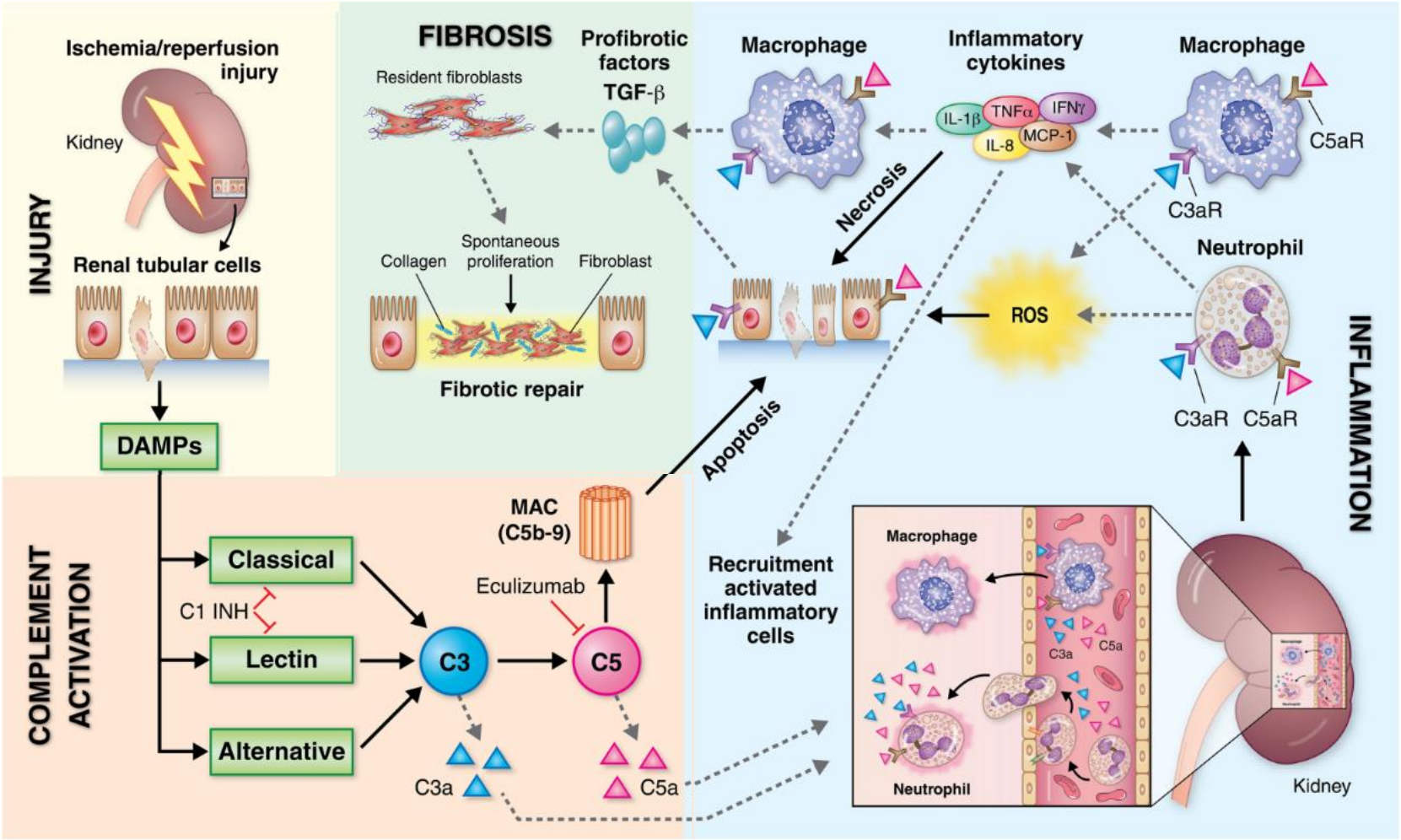


Colec11+/+ mice transplantated with kidneys from Colec11+/+ or Colec11-/-:
Colec11–/– transplants showed **strong protection from renal tubular** damage compared with that observed in *Colec11+/+ control transplants*



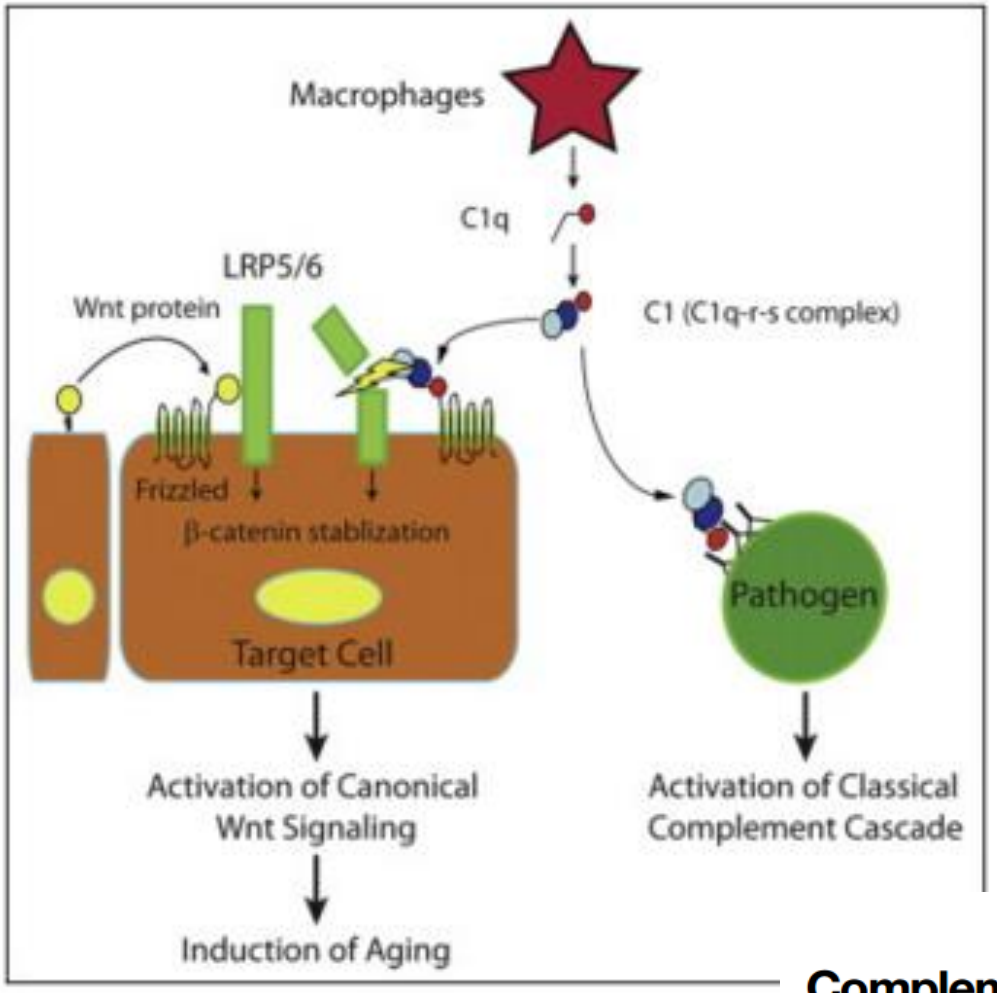
Farrar CA, Sacks SH, JCI 2016

Role of Complement in renal IRI



Danobeitia et al. Fibrogenesis & Tissue Repair 2014

Complement is bad for aging



- Augmented Wnt signaling is implicated in mammalian aging and aging-related phenotypes and fibrosis
- Serum C1q levels increase with aging
- The C1q complement protein is an activator of canonical Wnt signaling
- C1q-dependent Wnt signaling impairs the regenerative capacity of skeletal muscles

Cell

Complement C1q Activates Canonical Wnt Signaling and Promotes Aging-Related Phenotypes

Atsuhiko T. Naito, Tomokazu Sumida, Seitaro Nomura, Mei-Lan Liu, Tomoaki Higo, Akito Nakagawa, Katsuki Okada, Taku Sakai, Akihito Hashimoto, Yurina Hara, Ippei Shimizu, Weidong Zhu, Haruhiro Toko, Akemi Katada, Hiroshi Akazawa, Toru Oka, Jong-Kook Lee, Tohru Minamino, Toshio Nagai, Kenneth Walsh, Akira Kikuchi, Misako Matsumoto, Marina Botto, Ichiro Shiojima, and Issei Komuro*

RENAL GRAFT DETERIORATION

- Kidney transplantation is the best option for patients with ESKD;
- Despite improvements in first-year graft survival,

  long-term failure of kidney transplants remains an important clinical problem;
- There are several immunological and non-immunological factors related to renal graft deterioration, however several **histological lesions** of **chronic rejection** and **allograft nephropathy overlap** with those observed in **aging kidneys**

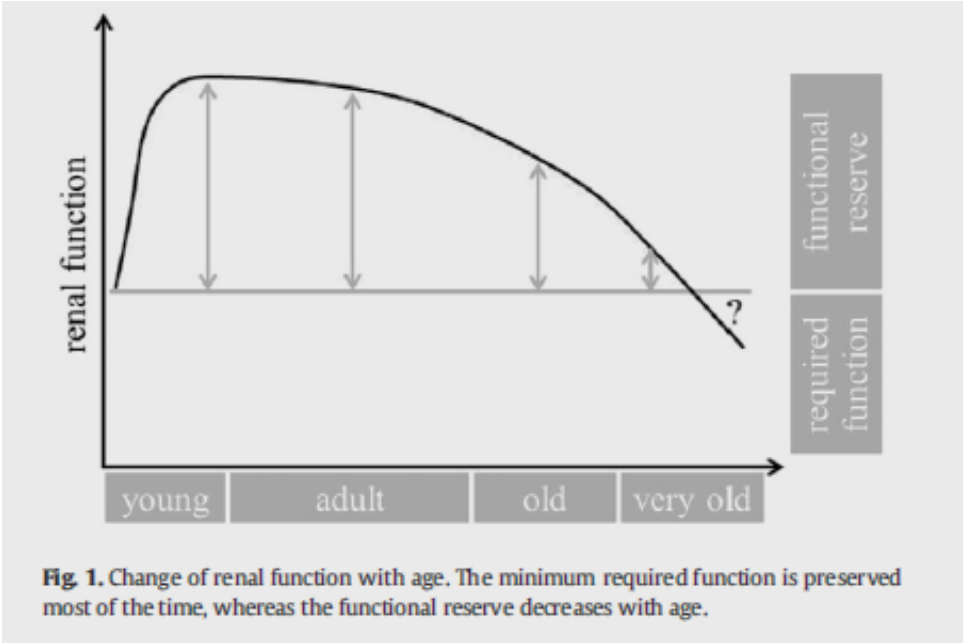
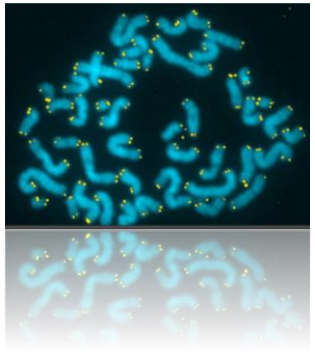


Fig. 1. Change of renal function with age. The minimum required function is preserved most of the time, whereas the functional reserve decreases with age.

Braun H; J Am Soc Nephrol (2012),

Gekle, M., Kidney and aging— A narrative review, Exp. Gerontol. (2016)

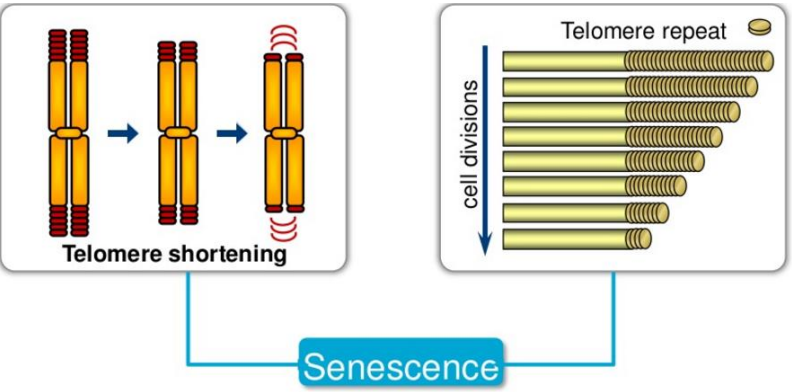
CELLULAR SENESCENCE



‘Originally described in human fibroblasts by Hayflick and Moorhead, ’ Cellular senescence’ describes a phenotype of permanent and irreversible growth arrest shown by mammalian cells.

Main mechanism are:

- Telomere shortening
- Cell cycle Inhibition



- A **telomere** is a region of repetitive nucleotide sequences at each end of a chromosome, which protects the end of the chromosome from degradation
- In humans, average telomere length declines from about 11kb at birth to less than 4 kb in old age
- In aging human kidney telomere shortening **is faster in cortex compared to medulla** (Melk A, JASN, 2000)

The American Journal of PATHOLOGY
Cellular and Molecular Biology of Disease
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Telomere Shortening and Cellular Senescence in a Model of Chronic Renal Allograft Rejection

S. A. Joosten, American Journal of Pathology, (2003)

Klotho: anti-aging gene

Nature. 1997 Nov 6;390(6655):45-51.

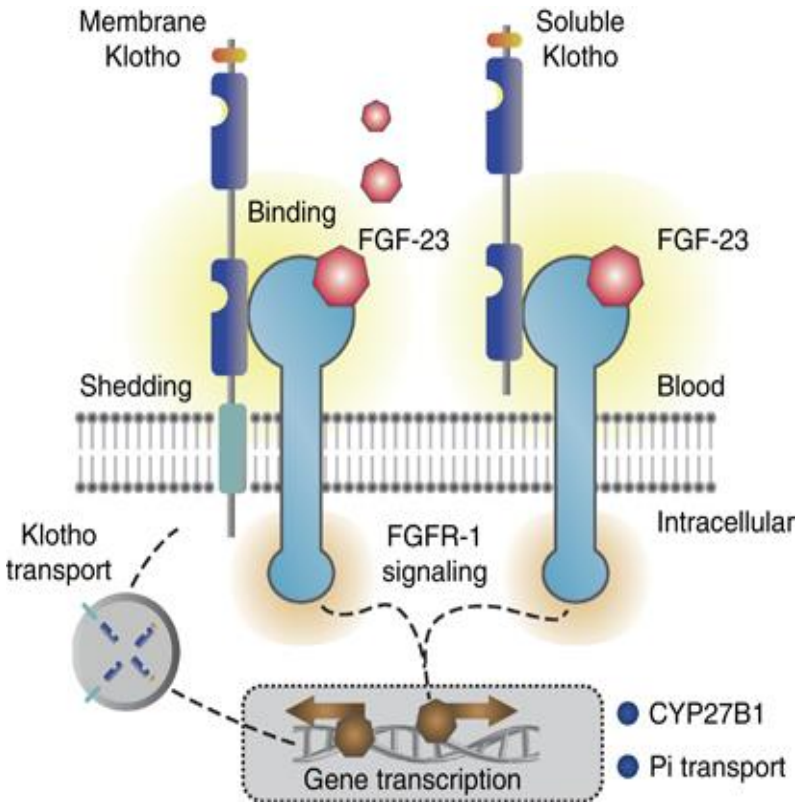
Mutation of the mouse klotho gene leads to a syndrome resembling ageing.

Kuro-o M[1], Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI.

A defect in Klotho expression in mice leads to a premature-aging syndrome.

Overexpression of Klotho extends life span in mice (by 20 and 30%)

Klotho: anti-aging gene

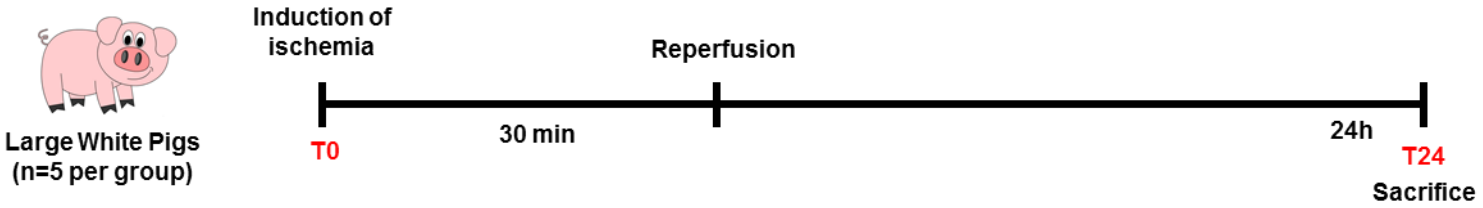


M.G. Vervloet and T. E. Larsson, KI 2011

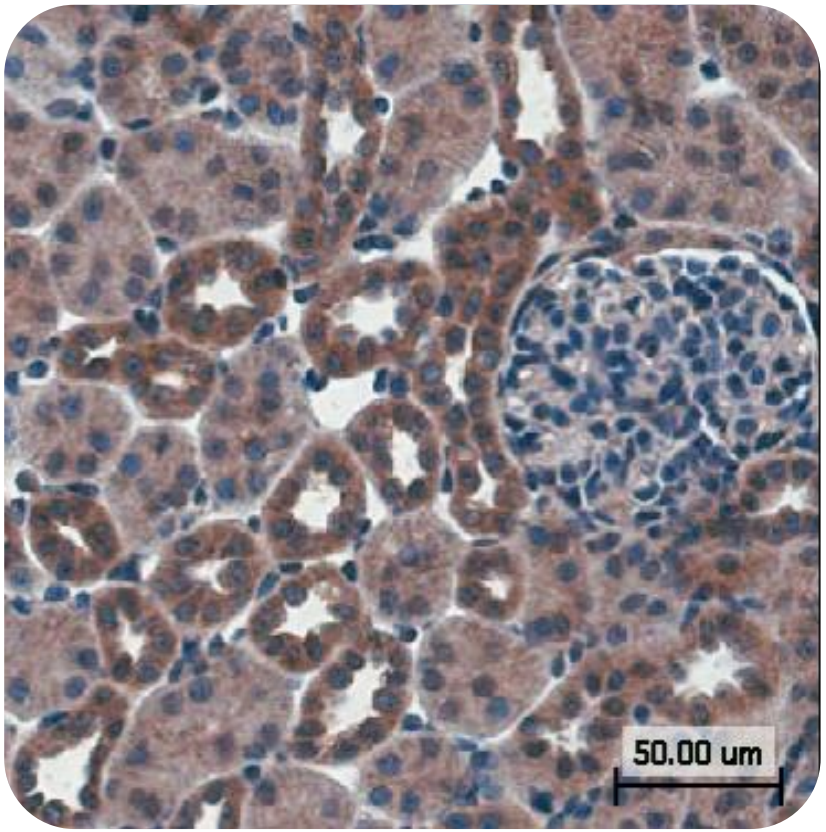
- α-Klotho is <u>mainly expressed in renal tubular cells</u>
- <u>Membrane form</u> regulates mineral homeostasis
- <u>Soluble form</u>, present in blood, urine and cerebrospinal fluid, acts as an endocrine factor interfering with renal and extrarenal functions

Hu et al. Nephrol Dial Transplant 2012
Wang Y. Ageing Res Rev 2009

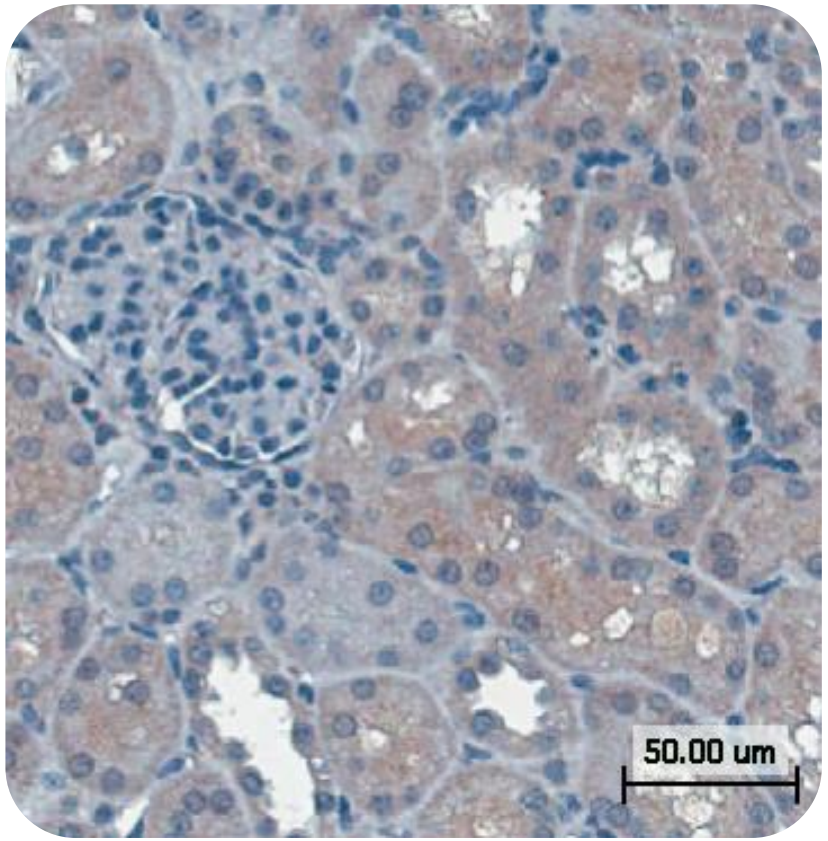
Klotho modulation in IRI



T0

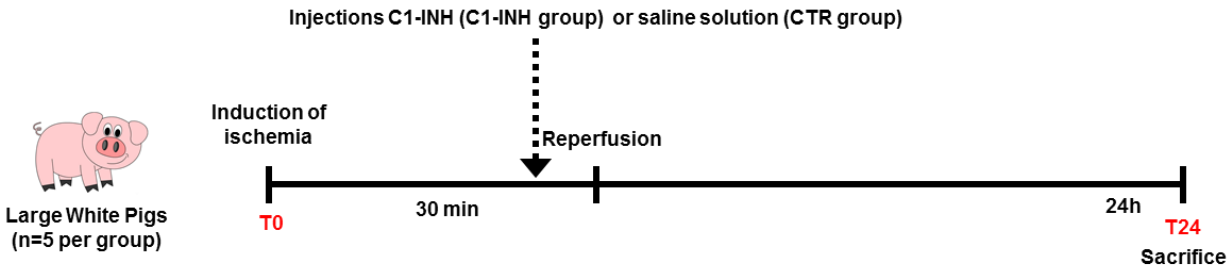


T24

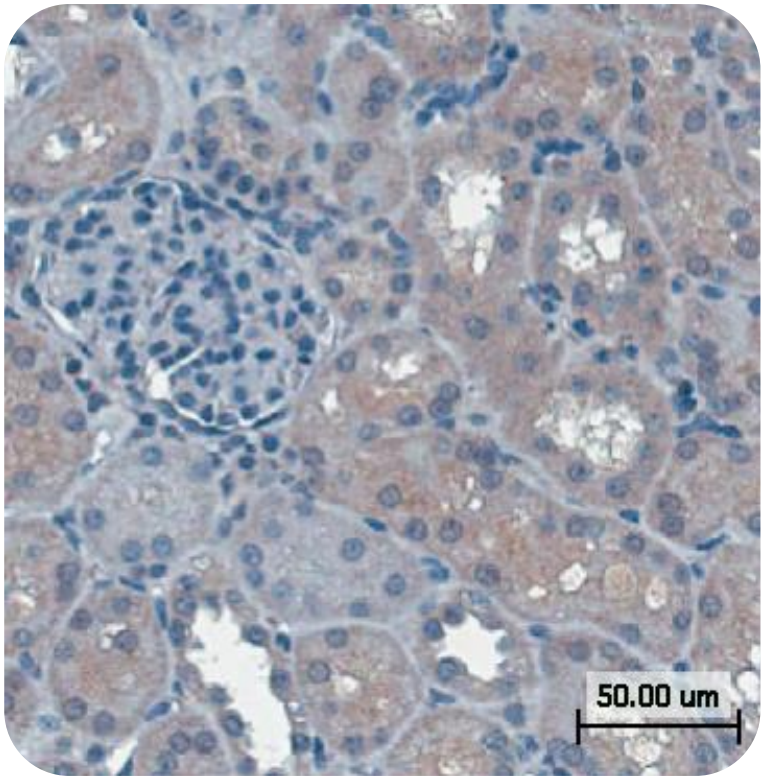


Castellano G, Intini A et al. Am J Transplant. 2016

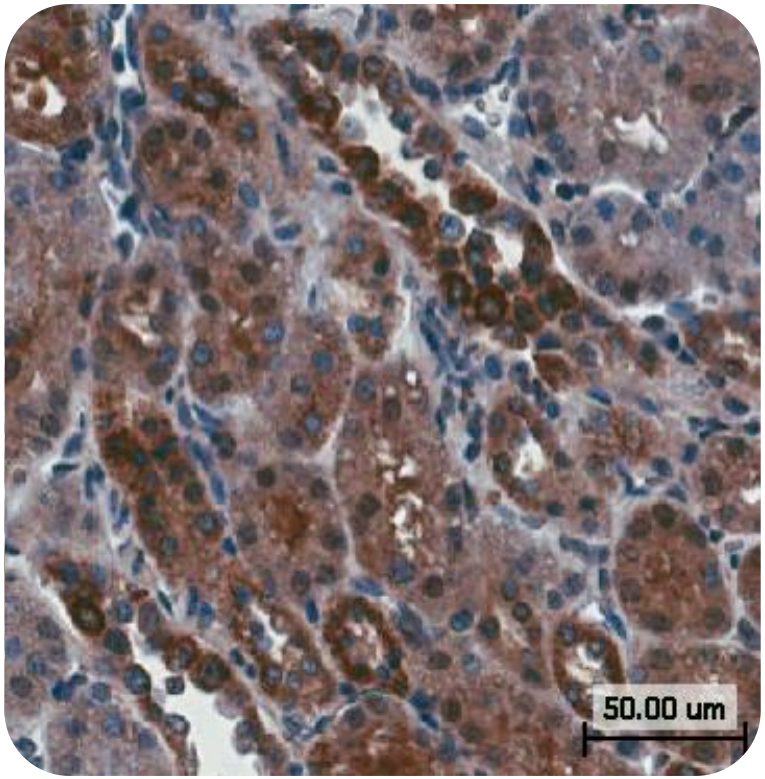
C1-INH treatment preserved renal Klotho



Ctr T24

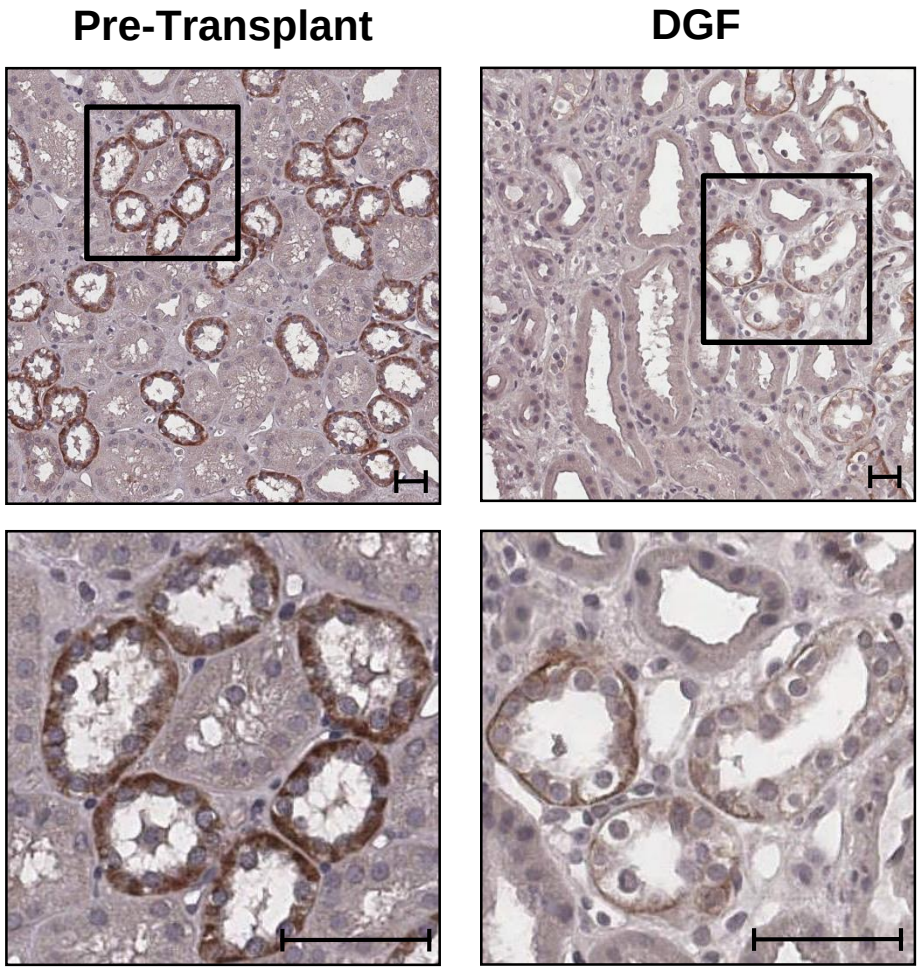


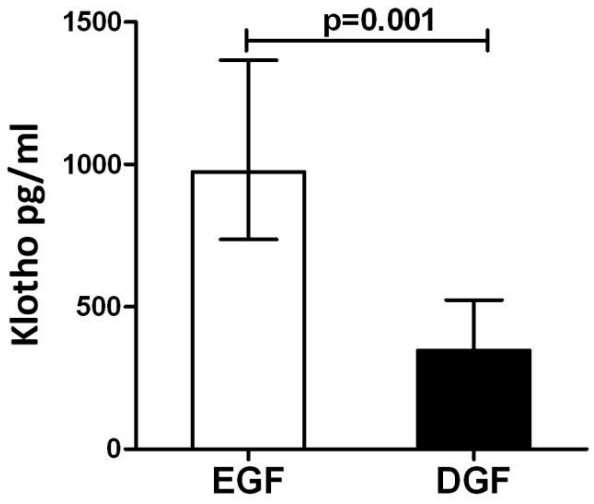
C1-Inh T24



Castellano G, Intini A et al. Am J Transplant. 2016

Klotho down-regulation in transplant recipients with DGF

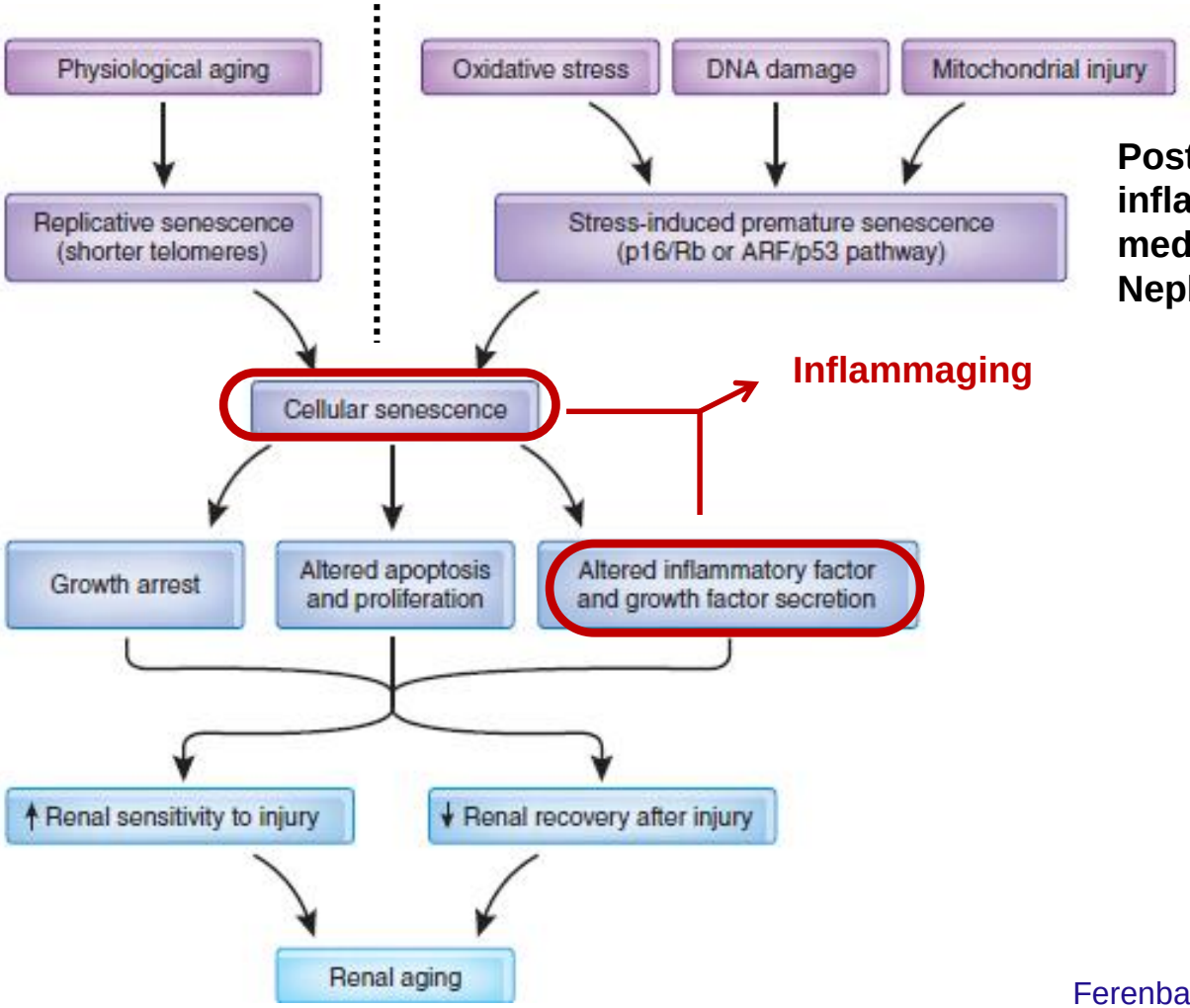




serum Klotho in DGF vs EGF patients at 2 years post-Transplant

Castellano G, Intini A et al. Am J Transplant. 2016

CELLULAR SENESCENCE: Inflammaging



Post-operative stress, inflammation, antibody mediated Rejection, Nephropathies, Diabetes

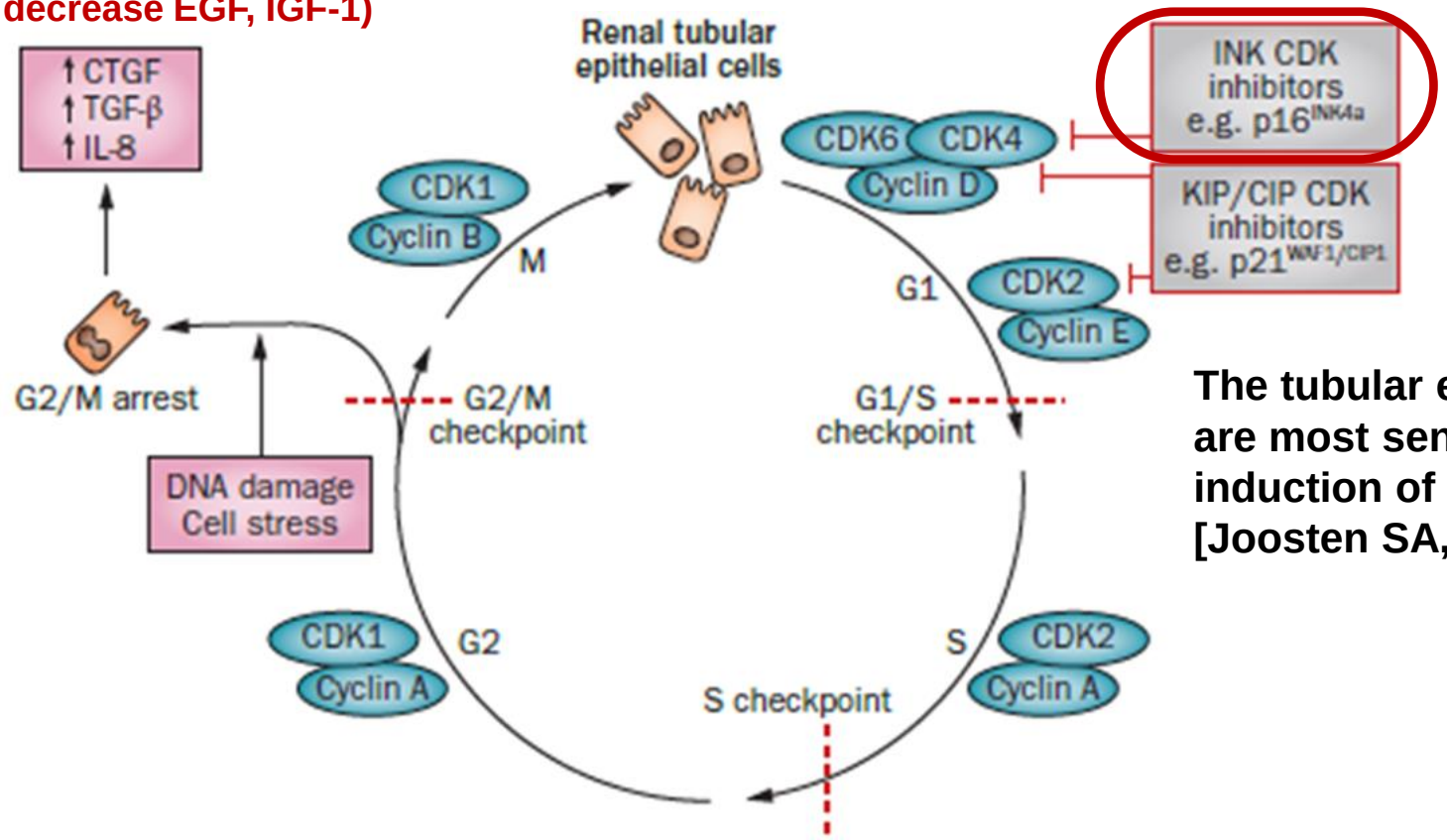
Ferenbach, D. A. ***Nat. Rev. Nephrol. 11 (2015)***

CELLULAR SENESCENCE

- Telomere shortening
- Cell Cycle Inhibition

SASP
(Senescence-Associated Secretory Phenotype)
increase IL-6, MCP-1, IL-1β
decrease EGF, IGF-1)

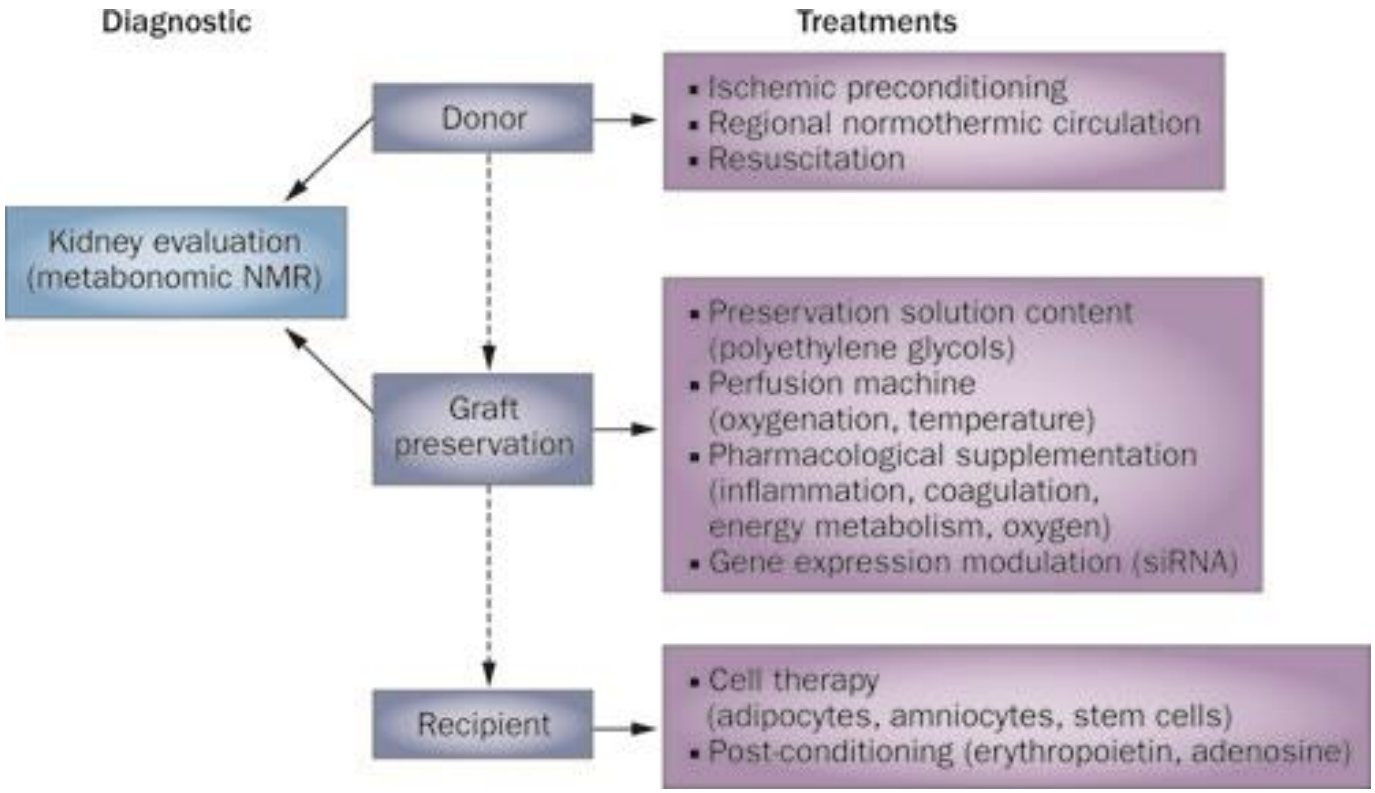
p16INK4a protein (gene CDKN2A) inhibits the activity of the cyclin-dependent kinases 4 and 6, leading to hypophosphorylation of the retinoblastoma gene and irreversible cell-cycle arrest



The tubular epithelial cells are most sensitive for the induction of senescence. [Joosten SA, KI 2004]

Ferenbach, D. A. & Bonventre, J. V. ***Nat. Rev. Nephrol. 11, 264–276 (2015);***

Figure 1 Innovative treatments at the donor, graft preservation or recipient levels to improve kidney recovery



Bon, D. *et al*. (2012) New strategies to optimize kidney recovery and preservation in transplantation *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2012.83

nature REVIEWS NEPHROLOGY

Adsorbimento: un possibile aiuto?

Controllando i livelli plasmatici di mediatori infiammatori, si potrebbero minimizzare i danni d'organo

IJAO
ISSN 0391-3988
Int J Artif Organs 2016; 00(00): 000-000
DOI: 10.5301/ijao.5000489
SHORT COMMUNICATION

First report of cytokine removal using CytoSorb® in severe noninfectious inflammatory syndrome after liver transplantation

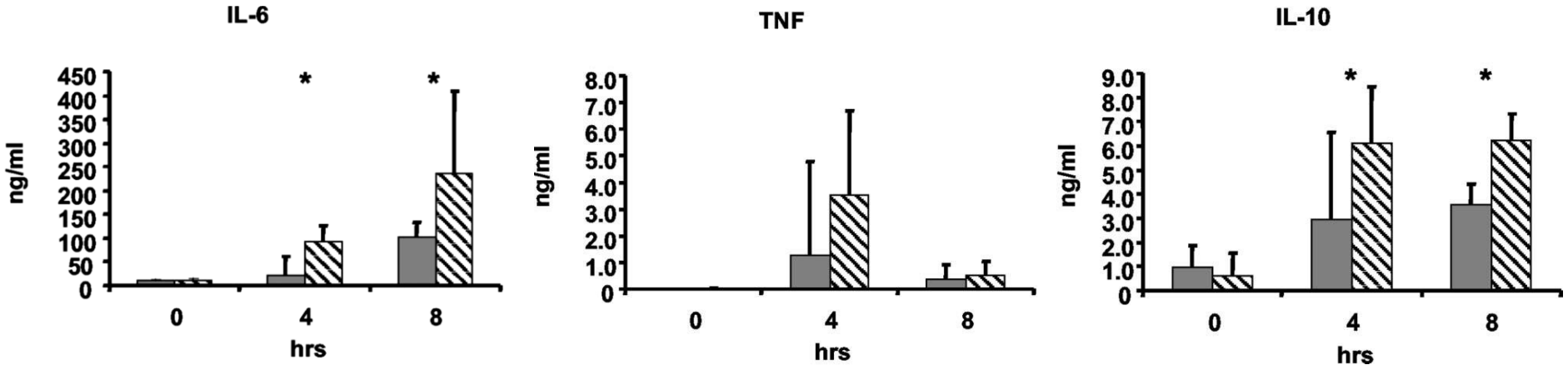
Dana R. Tomescu[1,2], Simona Olimpia Dima[3], Daniela Ungureanu[4], Mihai Popescu[2], Dan Tulbure[2,4], Irinel Popescu[2,3]

	GM-CSF	IFNg	IL-1b	IL-2	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10	IL-12p70	IL-13	MCP-1	TNFa
T1	7,55	0,50	8,73	30,53	14,37	<2.00	223,18	51,31	210,69	188,95	14,43	19,22	1963,67	45,49
T2	7,55	<2.49	8,96	37,81	12,66	<2.00	89,99	52,20	297,74	113,74	12,95	19,22	2369,63	49,70
T3	7,20	<2.49	6,62	40,35	13,23	<2.00	75,65	51,31	53,22	17,54	14,18	18,84	257,07	35,13
T4	5,22	<2.49	2,39	22,27	14,37	<2.00	56,95	51,31	119,90	61,34	12,95	18,45	509,99	62,71
T5	6,19	6,80	7,79	22,43	21,25	12,94	31,81	51,31	299,89	48,65	13,68	18,84	399,14	64,65
Mean M	5,38	0,50	2,62	21,81	13,92	12,94	7,25	26,54	20,20	14,23	12,79	18,07	281,61	16,09

Rimozione delle citochine In Vivo

Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-κB DNA binding, and improves short-term survival in lethal endotoxemia*

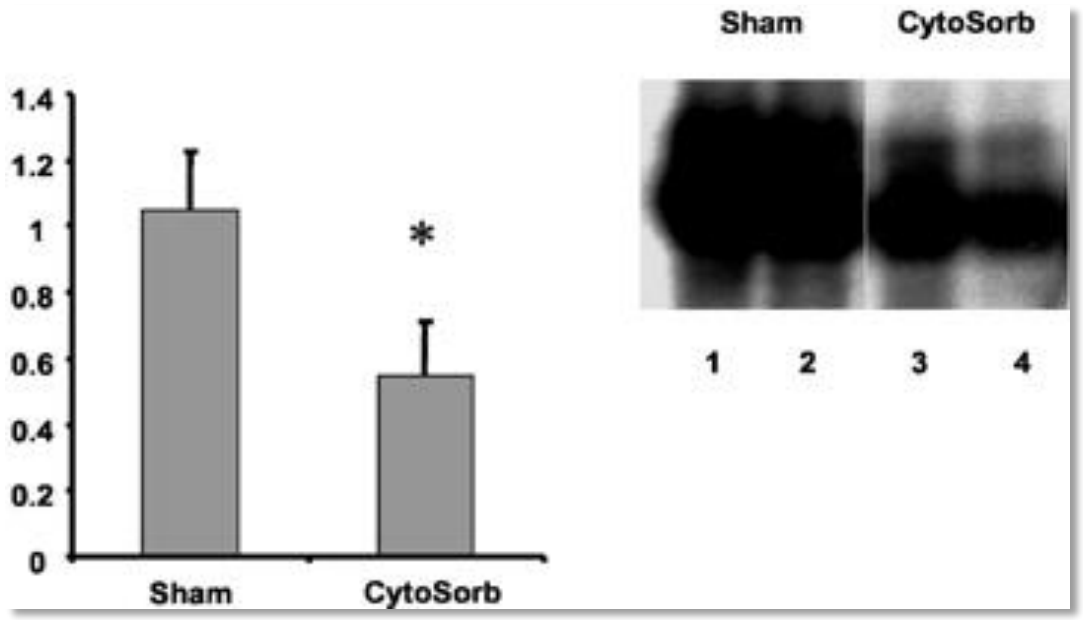
John A. Kellum, MD, FCCM; Mingchen Song, MD, PhD; Ramesh Venkataraman, MD



* Riduzione significativa di IL-6 e IL-10 ($p<.05$) in 8 h di emoperfusione con Cytosorb

Kellum, JA, Song M, Venkataraman, R "Hemoadsorption removes TNF, IL-6, and IL-10, reduces NF-KB DNA binding, and improves short-term survival in lethal endotoxemia" Crit Care Med (2004) 32(2): 801-805

Ridotta produzione di Citochine In Vivo



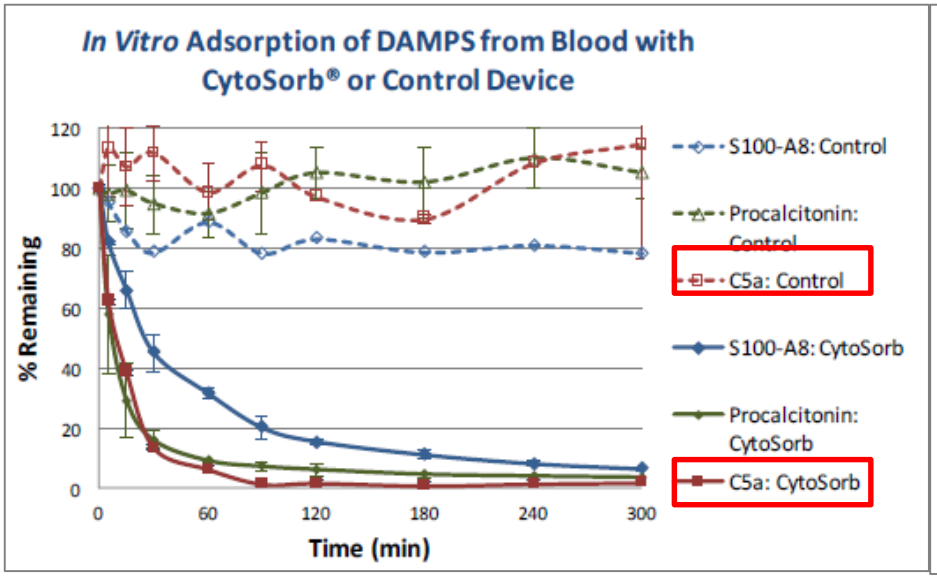
* p< .05

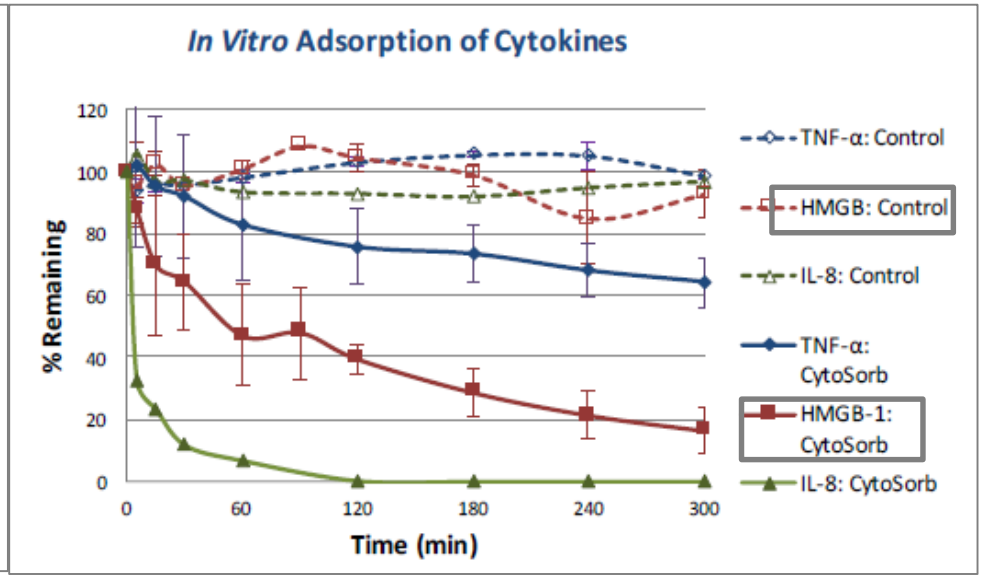
CytoSorb™ riduce sostanze, tra cui NF-κB, che determina la produzione di citochine.

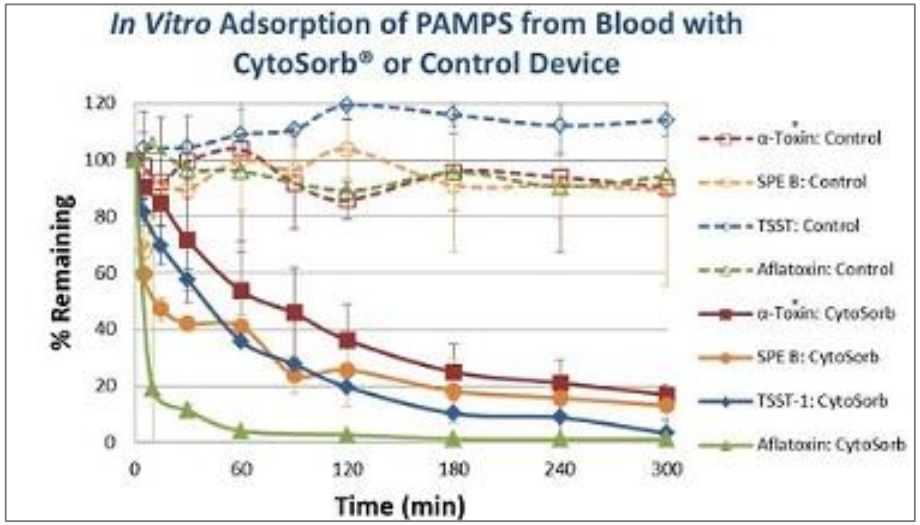
Kellum, JA, Song M, Venkataraman, R "Hemoadsorption removes TNF, IL-6, and IL-10, reduces NF-KB DNA binding, and improves short-term survival in lethal endotoxemia" Crit Care Med (2004) 32(2): 801-805

Rimozione PAMPS & DAMPS In Vitro

In vitro adsorption of a broad spectrum of sepsis inflammatory mediators with CytoSorb® hemoadsorbent polymer beads







Gruda et al. Crit Care 2016, Suppl

Cytokines

- ☑ MIP1-α
- ☑ IL-6
- ☑ IL-8
- ☑ IFN-ɣ
- ☑ TNF-α

DAMPS

- ☑ Complement (C5a, C3a)
- ☑ S100 proteins (S100A8, S100A9)
- ☑ Procalcitonin
- ☑ HMG-B1

Metabolites

- ☑ Pancreatic Trypsin, Chymotrypsin
- ☑ Free hemoglobin, myoglobin
- ☑ Bilirubin

PAMPS

Bacterial Exotoxins:

- ☑
  - Pneumolysin, Streptolysin
  - SPE B
  - TSST-1
  - STX-1, STX-2
  - Panton-Valentine leukocidin
- ☑ Hemolysins:
  - *Staph aureus α-toxin*
- ☑ Mycotoxins
  - *Aflatoxin*

Gruda et al. Crit Care 2016, Suppl

Table 1 Characteristics of current preservation solutions

Table 1 | Characteristics of current preservation solutions

Solution type	K^+ (mM)	Na^+ (mM)	Buffer (pH)	Impermeants	Adenosine (mM)	Antioxidants	Colloid
Intracellular type solution [K^+] >62 mM							
Belzer UW® (ViaSpan™)	125	30	Phosphate (7.3)	+	5	+	HES (50 g/l)
Intermediate type solution [K^+] 7–62 mM							
IGL-1®	30	125	Phosphate (7.3)	+	5	+	PEG 35 kDa (1 g/l)
KPS-1®	25	80	Phosphate HEPES (7.4)	+	5	+	HES (50 g/l)
Lifor™	16	98	Most commonly HEPES (7.1)	+	0.01	+	Dextran 70 and/or HES and/or other (45–55 g/l)
Celsior®	15	100	Histidine (7.3)	+	0	+	–
Polysol®	15	120	HEPES phosphate histidine (7.4)	+	5	+	PEG 35 kDa (20 g/l)
Custodiol® HTK	10	15	Histidine (7.2)	+	0	–	–
Extracellular type solution [K^+] <7 mM							
SCOT15®	5	118	Carbonate (7.4)	+	0	–	PEG 20 kDa (15 g/l)

Belzer UW® (Wisconsin Alumni Research Foundation, Madison, WI, USA); ViaSpan™ (DuPont Merck Pharmaceutical Company, Wilmington, DE, USA); IGL-1® (Institut Georges Lopez, Civrieux d'Azergues, France); KPS-1® (Lifeline Scientific, Itasca, IL, USA); Lifor™ (Lifeblood Medical, Freehold, NJ, USA); Celsior® (Genzyme Corporation, Cambridge, MA, USA); Polysol® (Doorzand Medical Innovations B.V., Amsterdam, The Netherlands); Custodiol® (Dr Franz Köhler Chemie GMBH, Alsbach-Hähnlein, Germany); SCOT15® (MacoPharma, Tourcoing, France). Abbreviations: HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HES, hydroxyethyl starch; PEG, polyethylene glycol; UW, University of Wisconsin.

Bon, D. *et al*. (2012) New strategies to optimize kidney recovery and preservation in transplantation
Nat. Rev. Nephrol. doi:10.1038/nrneph.2012.83

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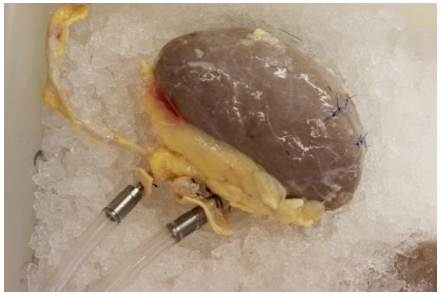
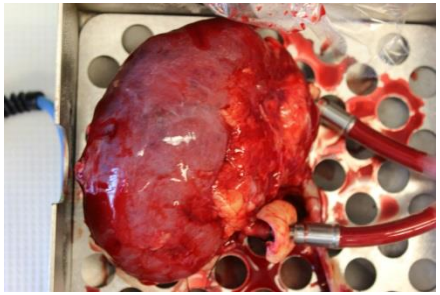
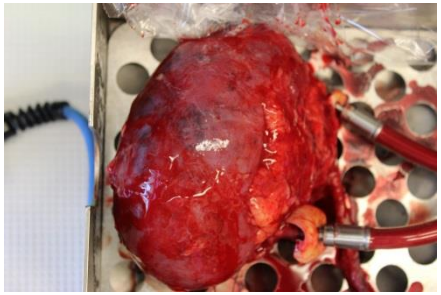
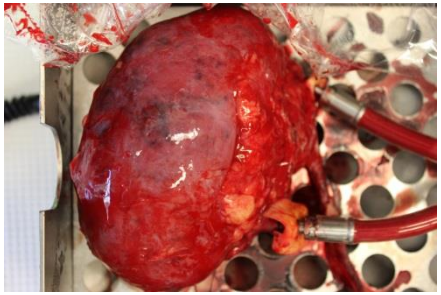
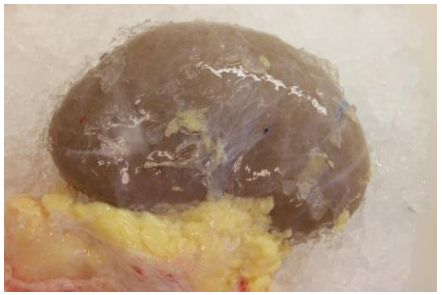
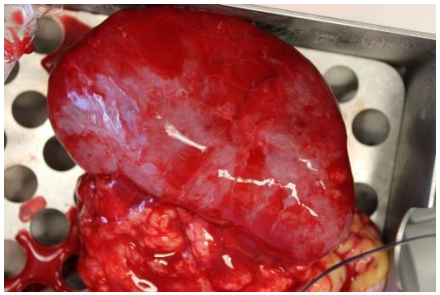
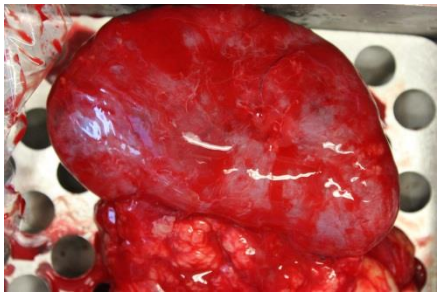
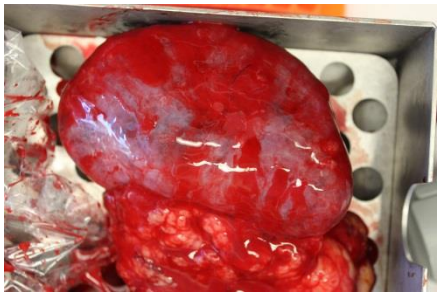
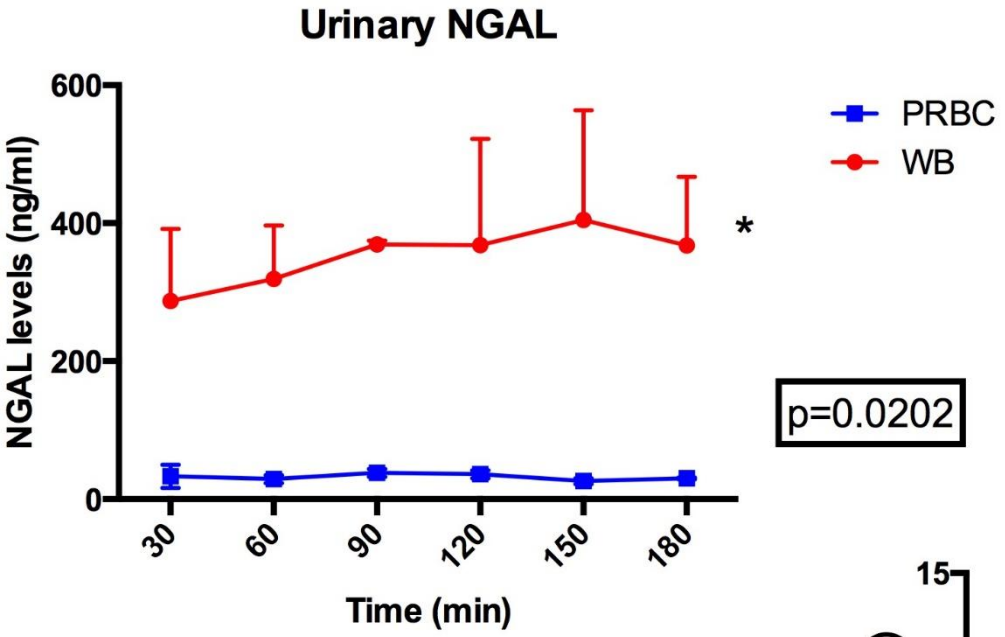
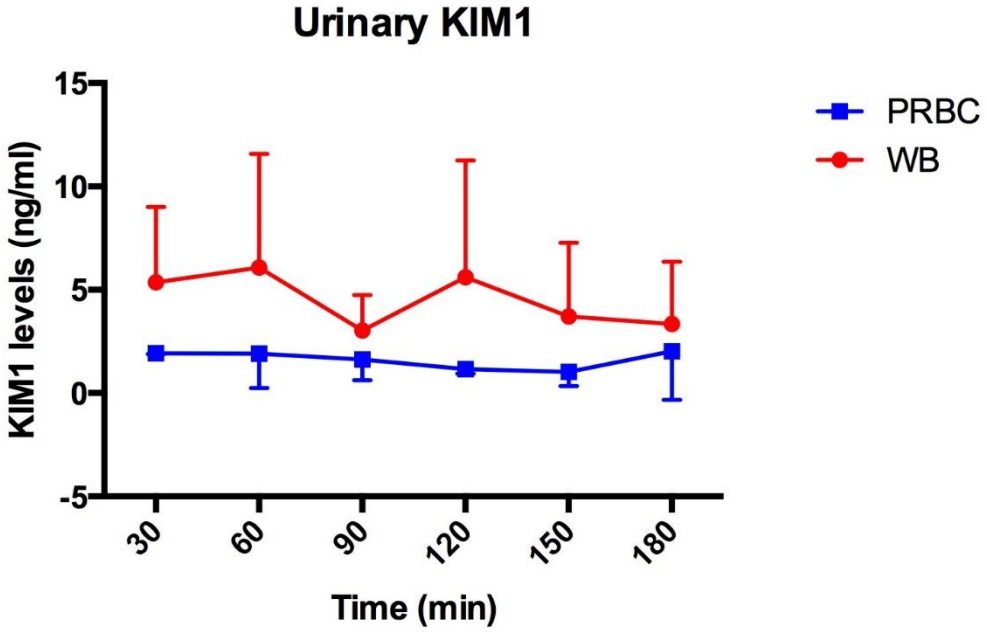
Human Kidney

Decreased injury biomarkers with optimized normothermic perfusion





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Thank you for your attention !