Aferetica
Purification Therapies

WORKSHOP

Purification Therapies

FROM RESEARCH TO CLINICAL EVIDENCE

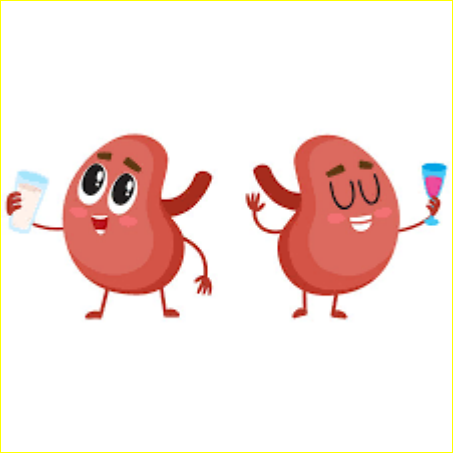
SEPTEMBER 30TH/OCTOBER 1ST 2022

Milano, Centro Congressi Cariplo

ESOT

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

EX VIVO PERFUSION AND INFLAMMATORY MEDIATORS
The Kidney



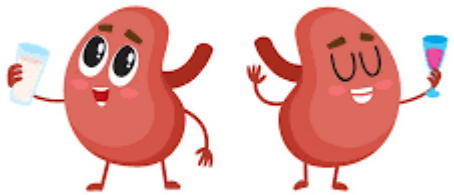
Vincenzo Cantaluppi

Nephrology and Kidney Transplantation Unit,
University of Piemonte Orientale (UPO),
"Maggiore della Carità" University Hospital,
Novara- ITALY

OUTLINE

UNIVERSITÀ DEL PIEMONTE ORIENTALE

Ex vivo Perfusion and Inflammatory Mediators: the Kidney



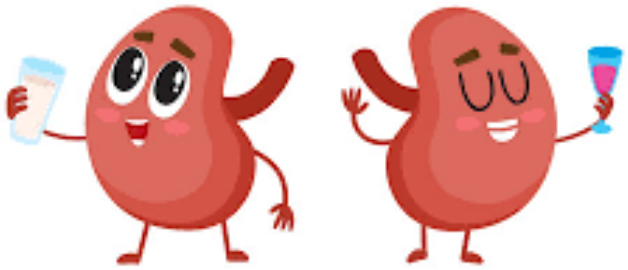
1. What are the aims of ex vivo perfusion?

2. What happens to inflammatory mediators during organ perfusion?

3. Inflammatory mediator removal during ex vivo perfusion: what are the impacts on perfusion and transplant outcomes?

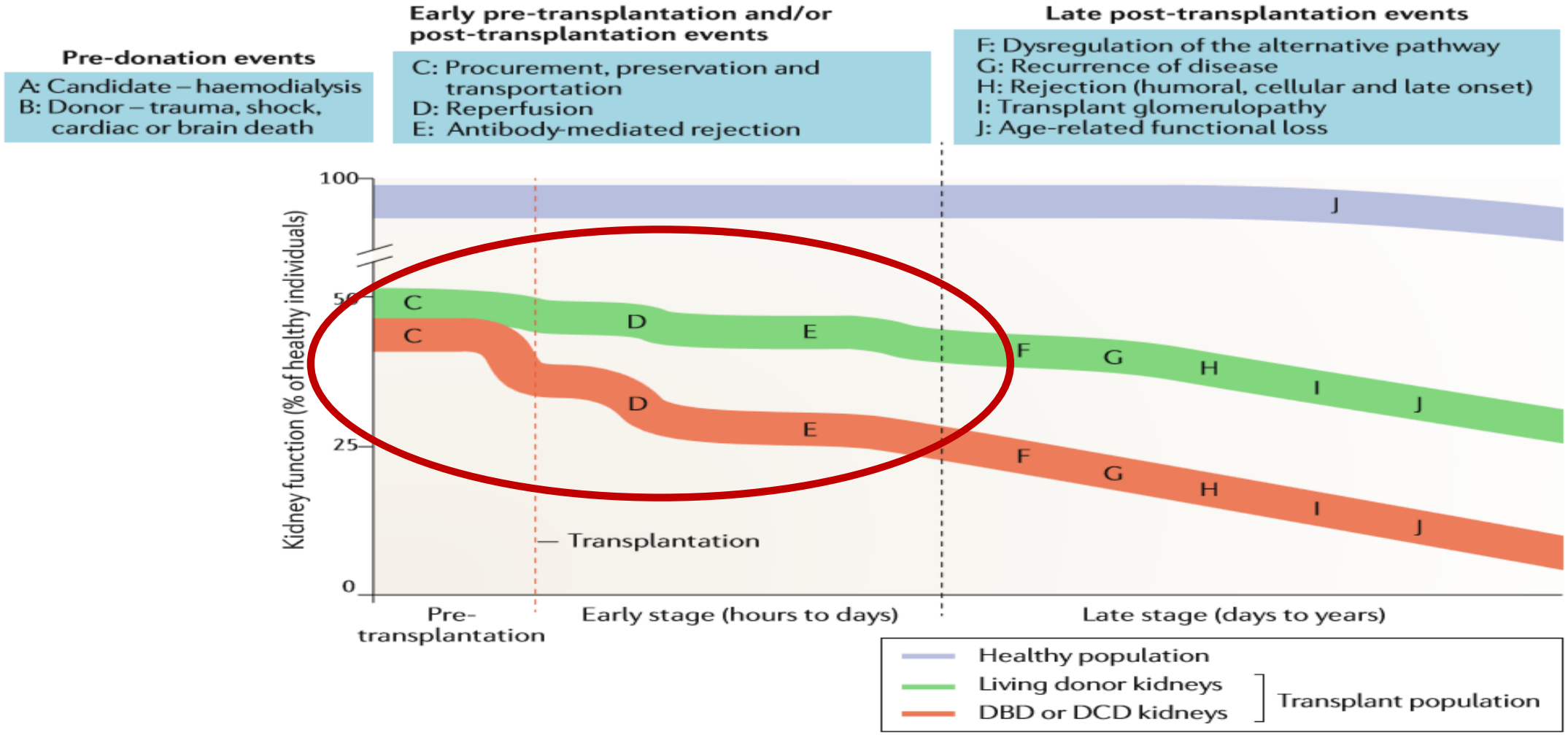
Machine perfusion

- Support of oxygen and nutrition
- Elimination of toxins/inflammatory mediators
- Decrease of vasospasm
- Endothelial vasoprotection
- Potential therapeutic intervention



Modified by Yuan X et al, *Transplant International*, 2010

Hypothetical model of time-course deterioration of kidney graft function



Biglarnia, Nat Review Nephrol 2018

Kidney Ex Vivo Perfusion – Why?

Recover all the organs available for transplantation
Extension of selection criteria:

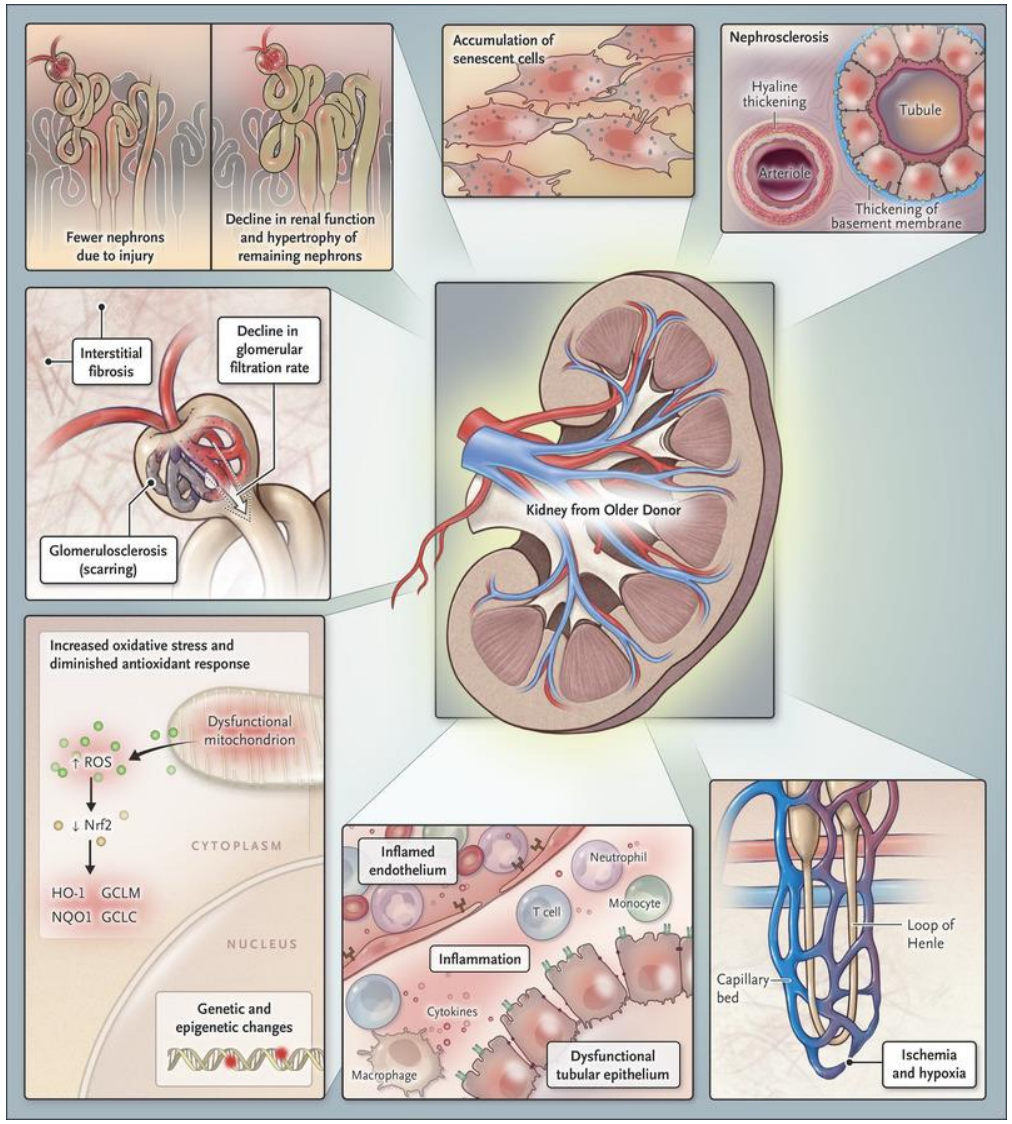
ECD and DCD organs for transplantation

Outcomes of kidney transplantation from different donor types (% range)

Donor type	DGF rate (%)	Graft survival at 1 y (%)	Graft survival at 5 y (%)	Patient survival at 1 y (%)	Patient survival at 5 y (%)
Living	2–19	96–98	85–92	98–99	93–95
DBD	10–28	89–97	80–85	96–99	82–89
ECD	28–38	82–92	49–80	90–96	70–93
DCD	23–58	85–92	77–87	95–99	82–89
uDCD	42–93	85–100	60–87	83–98	78–94

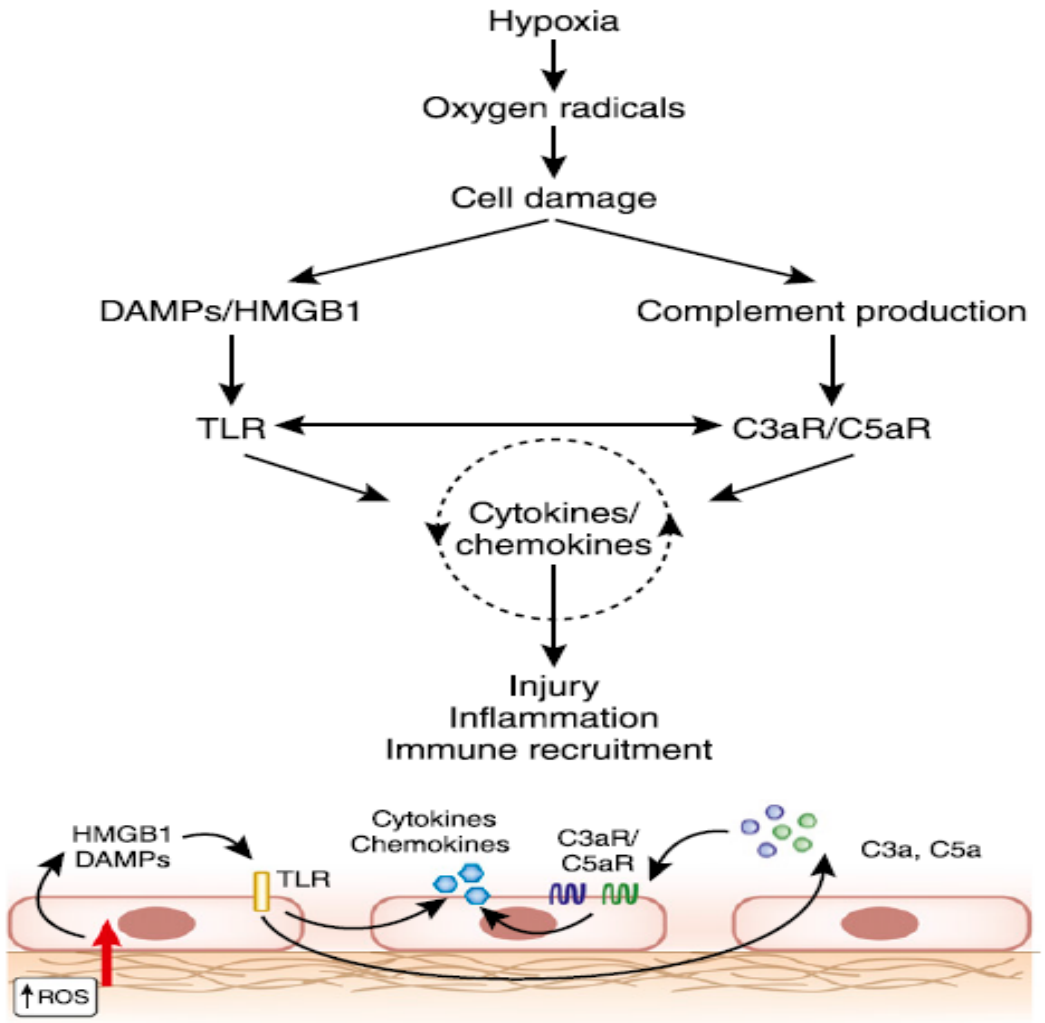
DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; ECD, extended criteria donor; uDCD, uncontrolled DCD

Higher complication rates and lower graft and patient survival



Renal Functional Reserve (RFR) decrease

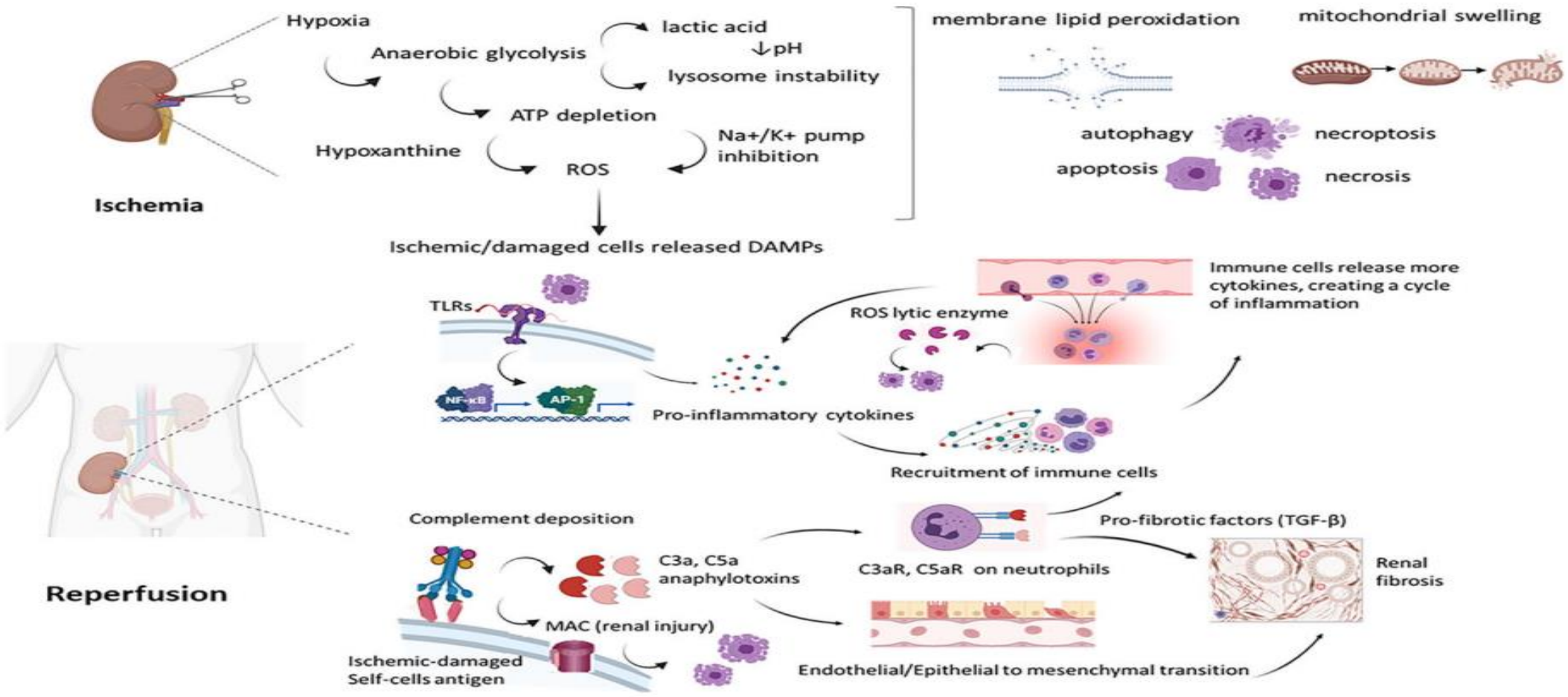
The pathophysiology of Renal IRI



- IRI arises from a combination of **tissue hypoxia, mitochondrial damage**, **ATP depletion** and **ROS generation**, leading to damage of the endothelium and epithelium and enhnaced **senescence.**
- Activation of neutrophils, release of ROS and other inflammatory mediators including adhesion molecules and a variety of cytokines are also involved.

Douglas R. Mathern and Peter S. Heeger, Clin J Am Soc Nephrol, 2015

Hypoxia, DAMPs, Pro-inflammatory Cytokines, Complement among the main responsables of IRI mechanisms



Machine Perfusion Therapy Delivery to Prevent IRI

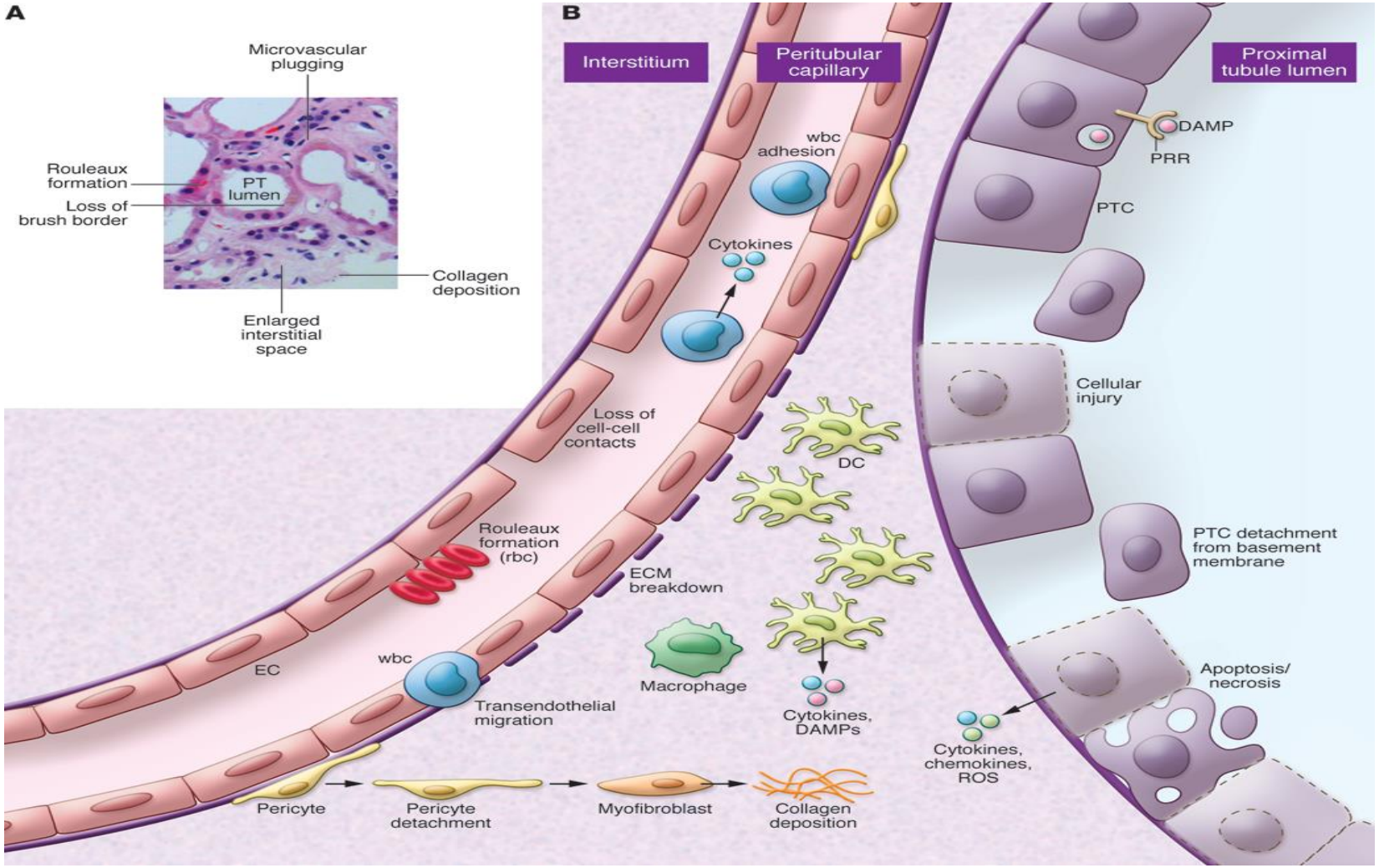
Franzin R, et al. Renal Delivery of Pharmacologic Agents During Machine Perfusion to Prevent Ischaemia-Reperfusion Injury: From Murine Model to Clinical Trials. Front Immunol. 2021.

Therapeutic translation in acute kidney injury: the epithelial/endothelial axis

Bruce A. Molitoris

JCI The Journal of Clinical Investigation
Published by The American Society for Clinical Investigation | Founded 1908

Alterations in the epithelial/endothelial axis during AKI



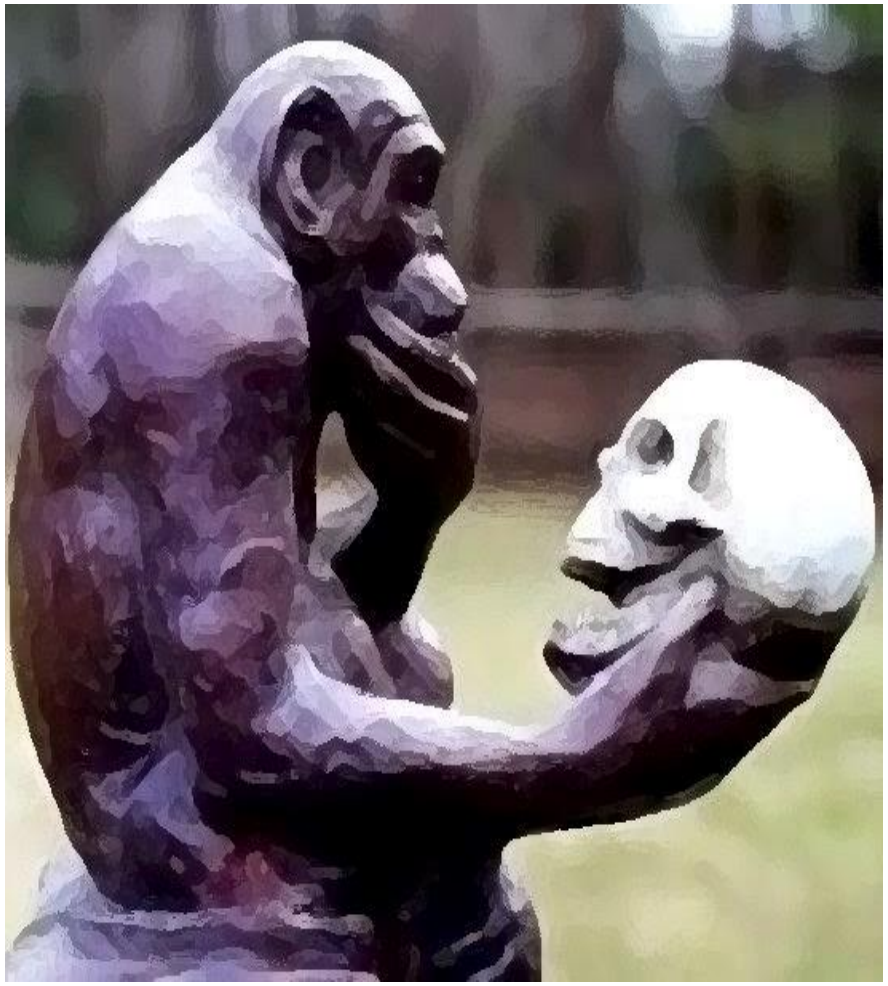
AKI

- **Endothelial dysfunction and microvascular rarefaction**
  - renal hypoxia
  - ↓ nitric oxide production
  - EndMT
  - Pericyte-myofibroblast transition
- **Incomplete regeneration of tubular cells**
  - EMT
  - G2/M cell cycle arrest and ↑ production of pro-fibrotic factors (TGF-ß, CTGF)
- **Persistent chronic inflammation**
  - switch M1→ M2 macrophage phenotype
  - ↑ complement cascade
  - Adaptive immune system response
- **Mitochondrial dysfunction**
- **Epigenetic modifications**
  - DNA methylation
  - histone changes
  - expression of specific microRNA
- **RAS activation**
  - ↑ urinary angiotensinogen as AKI-to-CKD biomarker
- **Cell and tissue senescence**
  - activation of pro-senescent molecules (p21, p16/*NK*4α)
  - ↓ α-Klotho levels

CKD

Fiorentino et al. Contrib Nephrol 2018

Inflammatory cytokines……



Biomarkers or mediators?

Role of Inflammatory Cytokines in Kidney DGF

Original Paper Ann Transplant, 2009; 14(4): 12-15

Table 1. Results in particular time intervals and depending on taking up function by the grafted organ (GGF, DGF, Sum.-summary), presented as mean ± standard deviation (SD).

	CRP (µg/ml)			Il-1b (pg/ml)			TNFα (pg/ml)			Il-6 (pg/ml)		
	GGF	DGF	Sum.	GGF	DGF	Sum.	GGF	DGF	Sum.	GGF	DGF	Sum.
P0	5.04±3.3	14.71±6.6	10.28±9.3	9.98±4.8	7.88±3.7	8.84±5.2	46.97±19.1	65.6±26.7	57.07±24	10±3.6	13.5±2.9	11.9±3.2
P1	10.06±7.6	15.45±9.1	12.98±5.4	13.05±3.6	8.58±3.9	10.63±4.1	22.96±16.3	51.28±21.4	38.3±19.2	83.7±23.3	60.9±26.3	71.4±28.4
P2	10.37±6.9	11.32±3.8	10.89±4.7	7.65±2.7	9.67±4.6	8.74±6.1	25.69±14.2	19.44±16.5	22.3±15.1	12.9±3.8	7.8±2.1	10.2±2.7

Delayed Graft Function associated with

CRP

IL-1β

Organs Deterioration predicted by

IL-6

IL-18

Suszka-Świtek et Al., Ann Transplant 2009

Interaction between systemic inflammation and renal tubular epithelial cells

Vincenzo Cantaluppi, Alessandro Domenico Quercia, Sergio Dellepiane, Silvia Ferrario, Giovanni Camussi and Luigi Biancone

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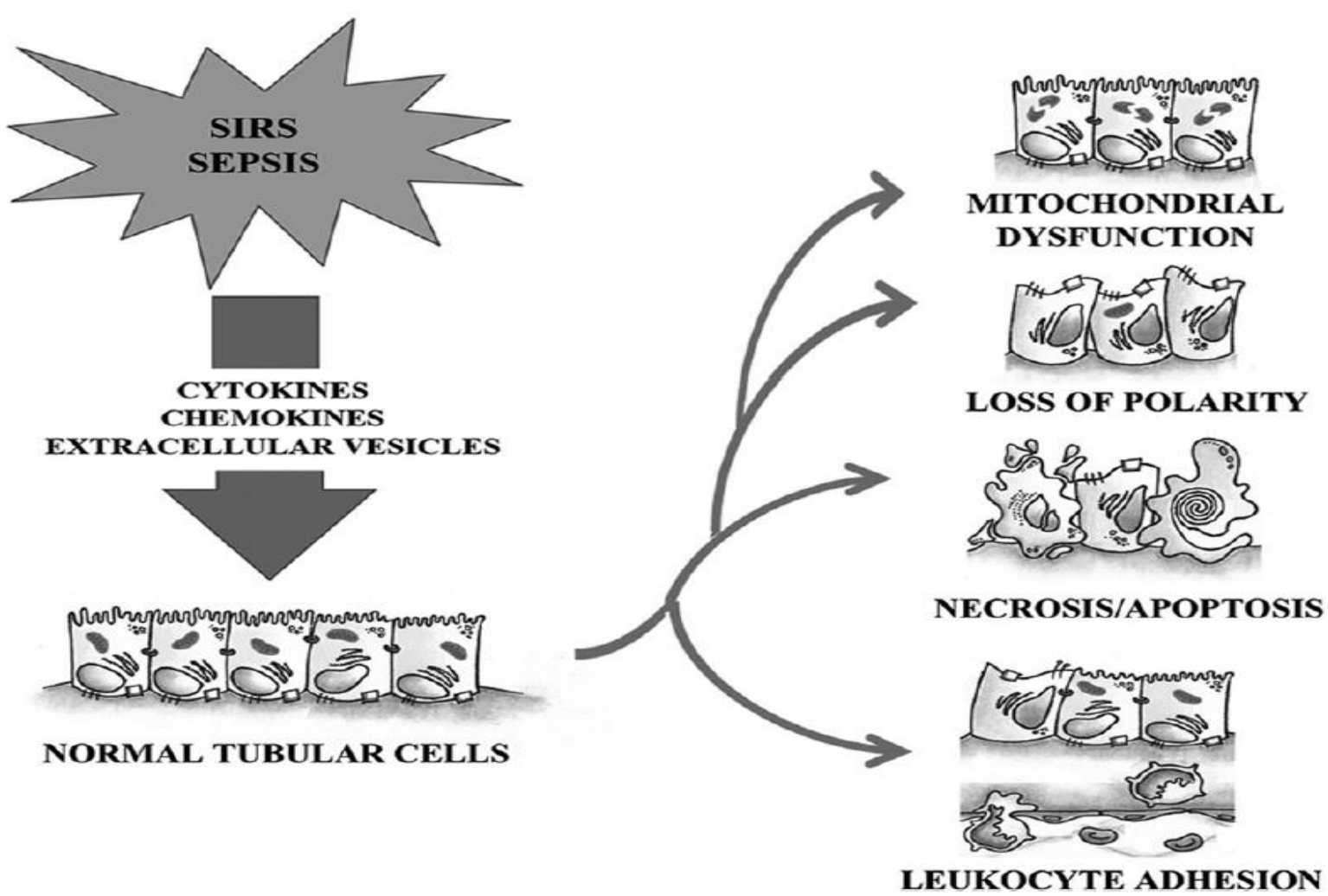
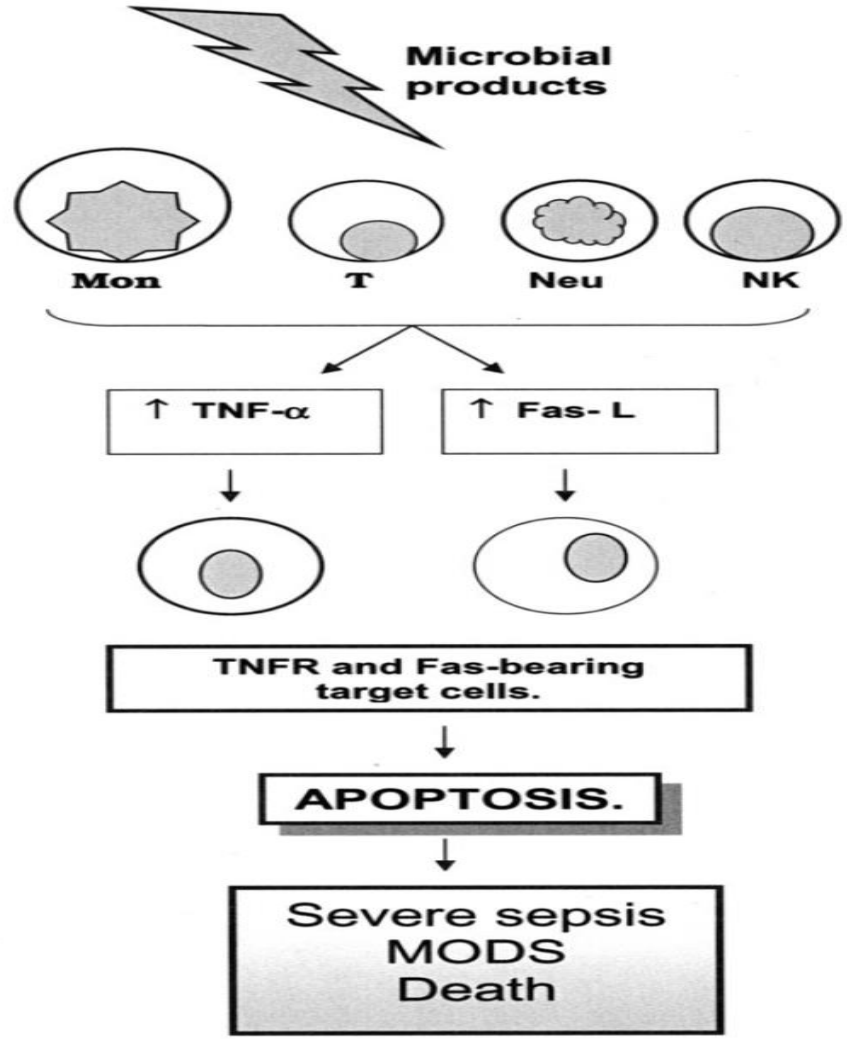
Nephrology Dialysis Transplantation

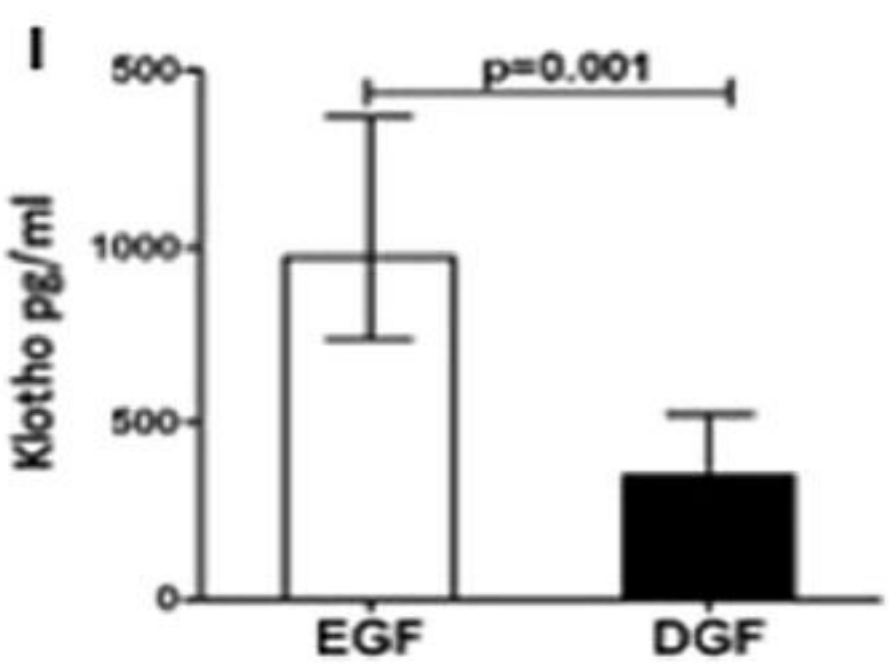


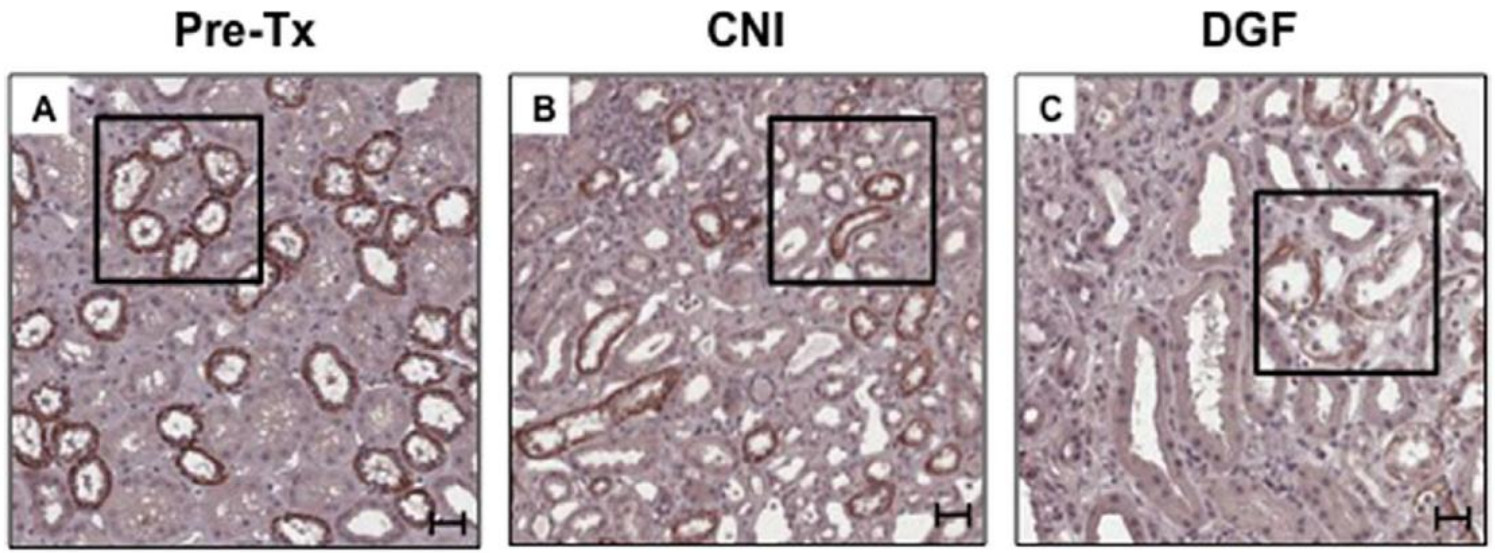


Complement Modulation of Anti-Aging Factor Klotho in Ischemia/Reperfusion Injury and Delayed Graft Function

G. Castellano[1,*,†], A. Intini[1,†], A. Stasi[1], C. Divella[1], M. Gigante[1], P. Pontrelli[1],

Klotho down-regulation in kidney transplant recipients with DGF





Inflammaging and Complement System: A Link Between Acute Kidney Injury and Chronic Graft Damage

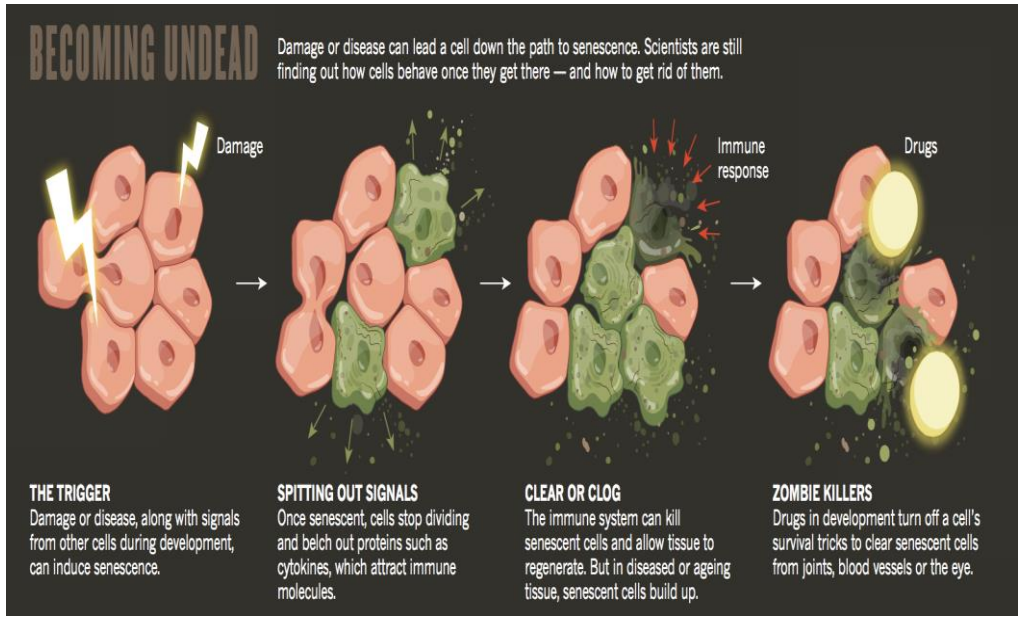
Rossana Franzin[1,2], Alessandra Stasi[1], Marco Fiorentino[1], Giovanni Stallone[3], Vincenzo Cantaluppi[2], Loreto Gesualdo[1] and Giuseppe Castellano[1,3]**

Identification of Molecular Markers of Delayed Graft Function Based on the Regulation of Biological Ageing

Dagmara McGuinness[1], Johannes Leierer[4], Olivier Shapter[1], Suhaib Mohammed[1], Marc Gingell-Littlejohn[1], David B. Kingsmore[2], Ann-Margaret Little[3], Julia Kerschbaum[4],

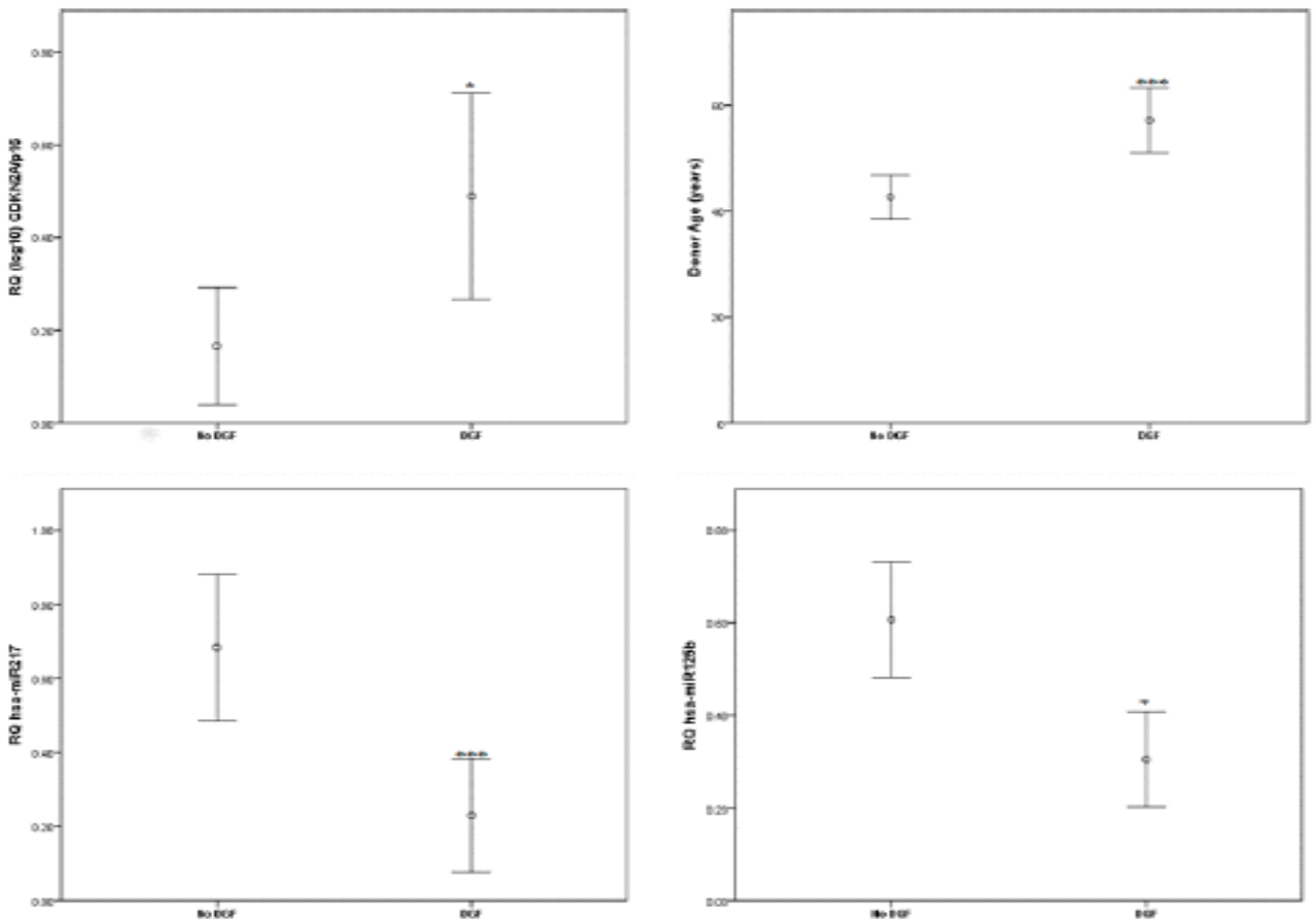
PLOS ONE

Delayed graft function is related to donor age, CDKN2A/p16 and the expression of hsa-miR-217 and hsa-miR-125b.



Senescent cells: an emerging target for diseases of ageing

Bennett G. Childs[1], Martina Gluscevic[1], Darren J. Baker[1,2], Remi-Martin Laberge[3], Dan Marquess[3], Jamie Dananberg[3] and Jan M. van Deursen[1,2]



1968 – Belzer's Transportable renal perfusion unit and first characterizations

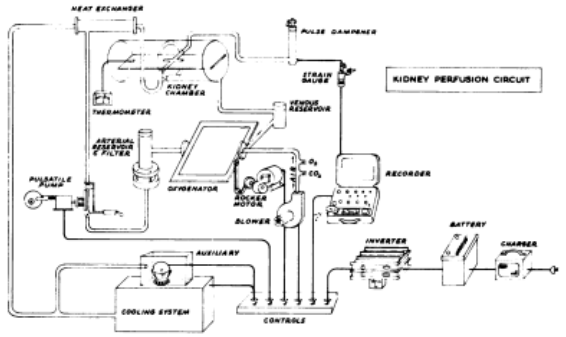
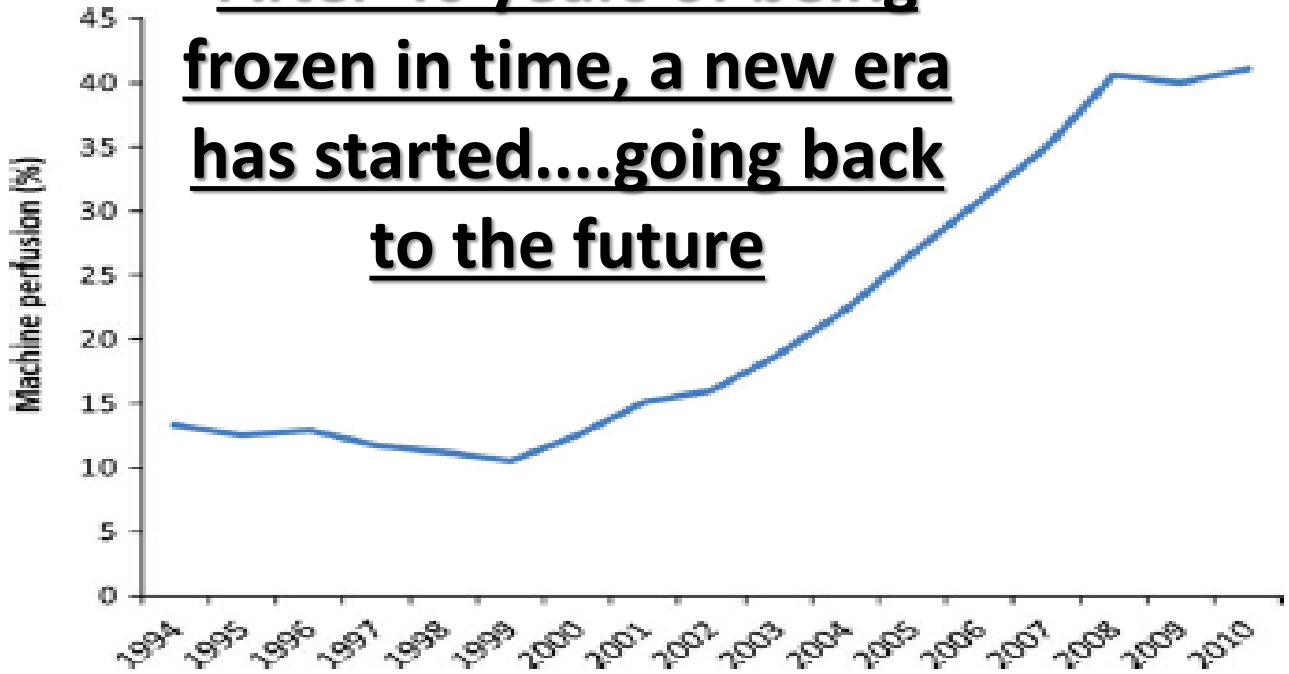


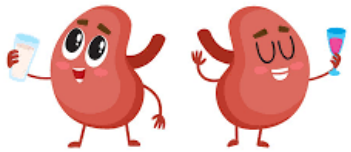
FIG. 4. Diagram of transportable renal preservation unit.

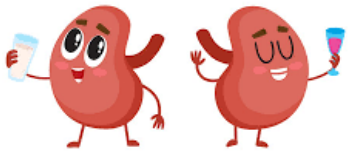
After 40 years of being frozen in time, a new era has started....going back to the future



A transportable perfusion circuit, which utilizes a membrane oxygenator, pulsatile pump, and hypothermia has been used successfully in human cadaver transplants as well as in animal experiments.

Machine Perfusion Therapy Delivery for Organ Resuscitation, Repair, Rejuvenation, Regeneration





THE ROLE OF OXYGENATION

THE ROLE OF TEMPERATURE

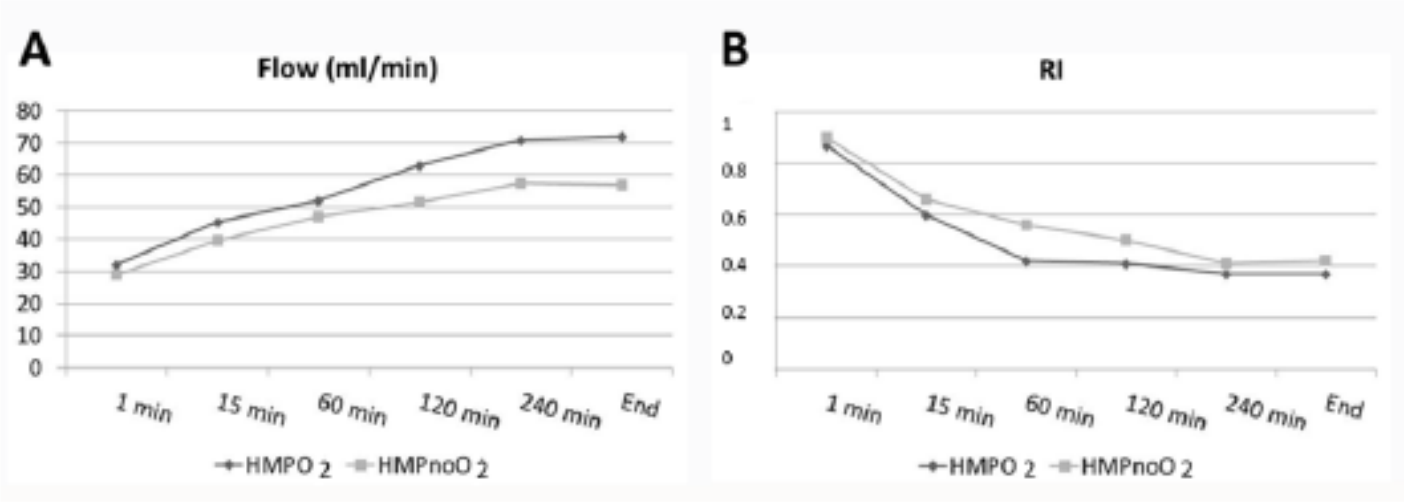
THE ROLE OF IMMUNOMODULATION

ANIMAL MODELS

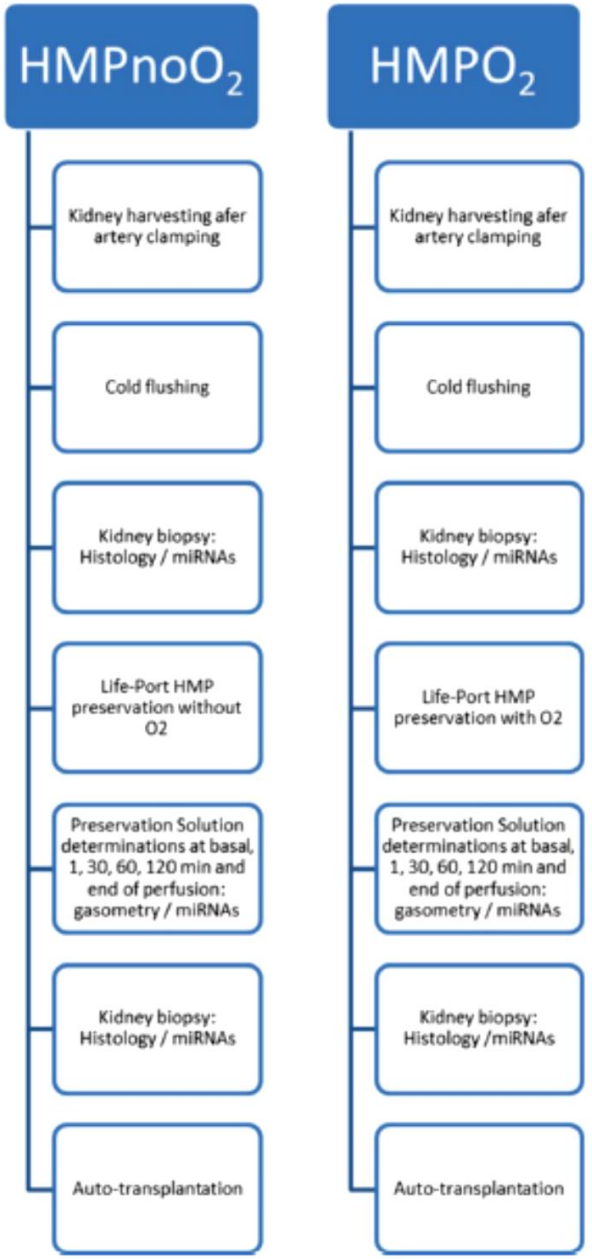
The role of Oxygenation: Is It Time to take a Breath?

MicroRNAs as Potential Markers for Advantageous Perfusion in a Preclinical Donation after Cardiac Death Animal Model of Oxygenated Hypothermic Machine Perfusion (HOPE)

Randomized not blinded prospective cohort study
Pig model
Maastricht type III DCD
5 $HMPO_2$ VS 7 $HMPnoO_2$



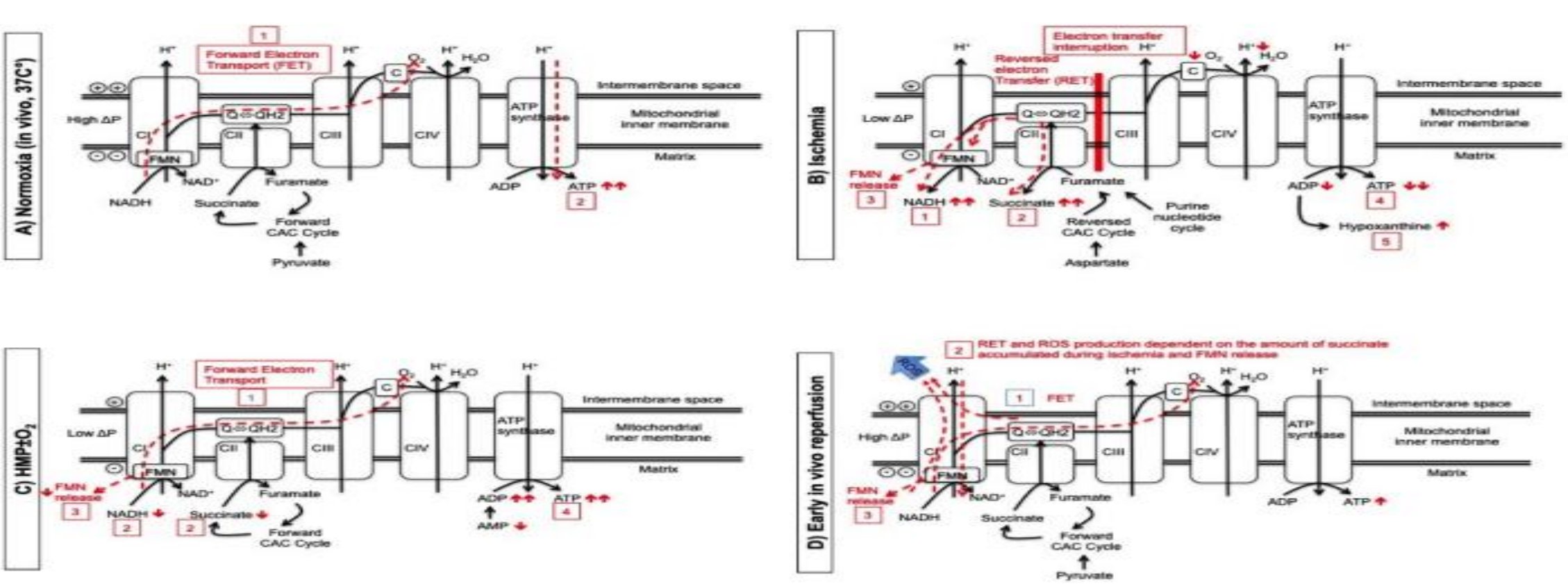
A trend of increasing graft function and survival in O_2 group was observed



Dos-Santos et al. OBM Transplantation **2018**, Volume 2, Issue 2
doi:10.21926/obm.transplant.1802012

Basic Parameters –
The role of Oxygenation: Is It Time to take a Breath?

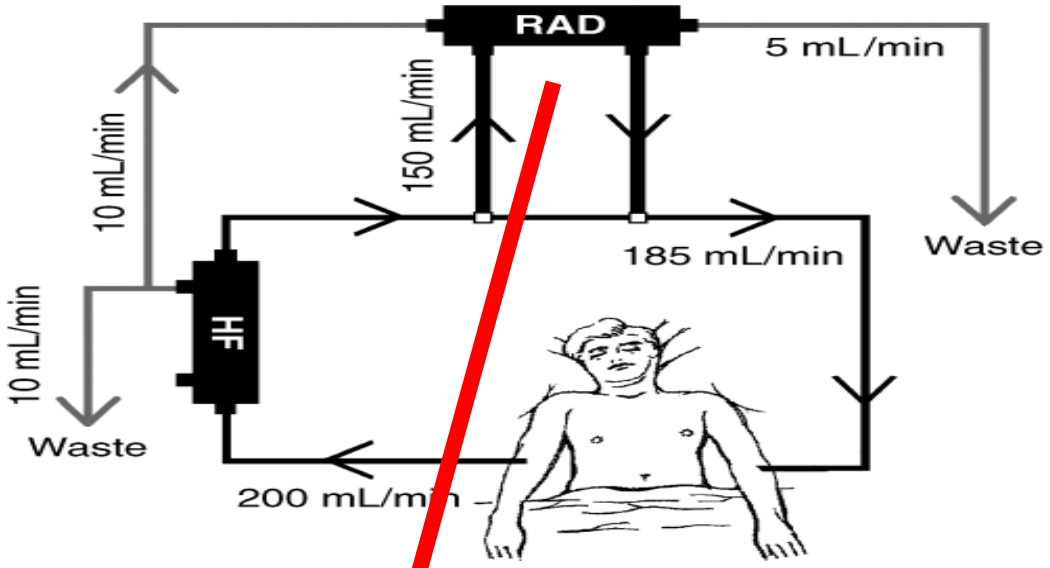
Active Oxygenation to Reduce IRI

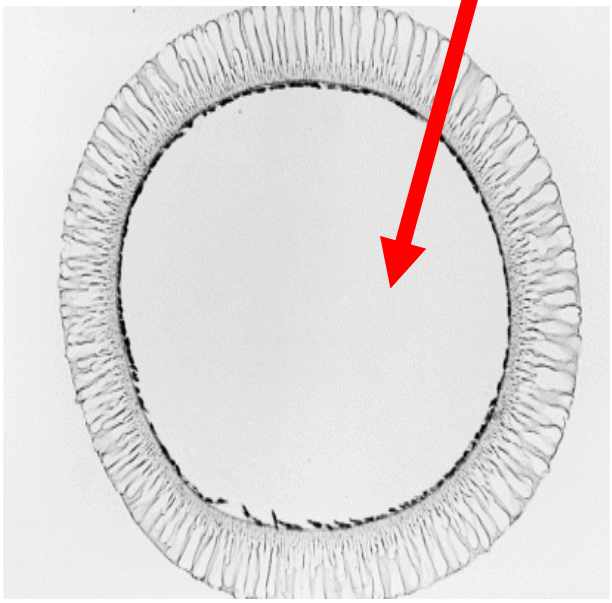


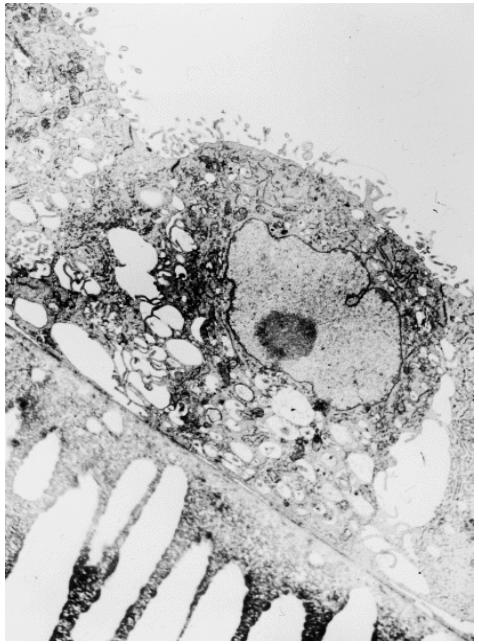
Under oxygen supplemented conditions, the diffusion of oxygen into the HMP perfusion fluid promotes physiological mitochondrial processes with evidence of FET activity

Darius, T.; Nath, J.; Mourad, M. Simply Adding Oxygen during Hypothermic Machine Perfusion to Combat the Negative Effects of Ischemia-Reperfusion Injury: Fundamentals and Current Evidence for Kidneys. Biomedicines 2021, 9, 993. https://doi.org/ 10.3390/biomedicines9080993

RAD: Renal Assist Device
H.D. Humes, University of Michigan



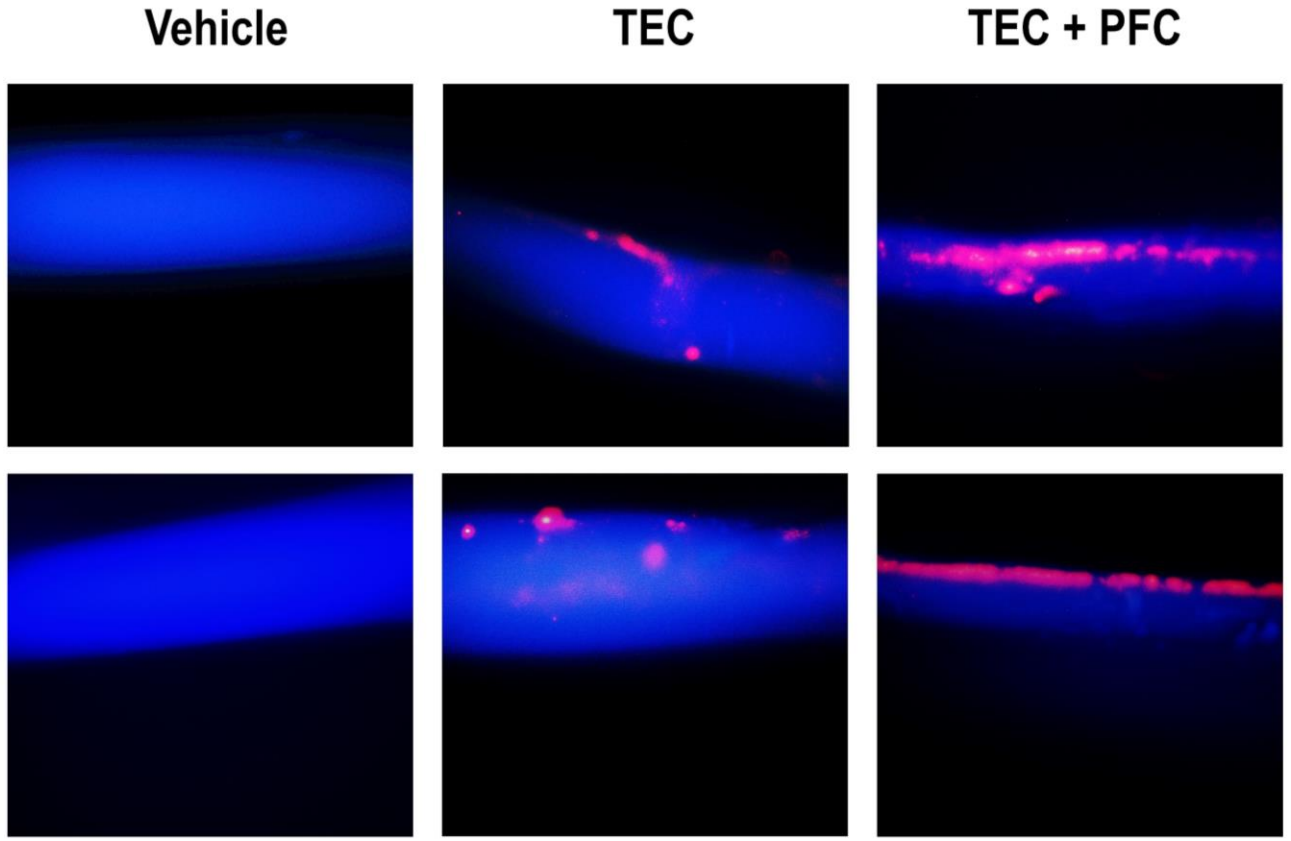




Nephrol Dial Transplant (2017) 1–12
doi: 10.1093/ndt/gfx328

ndt
Nephrology Dialysis Transplantation

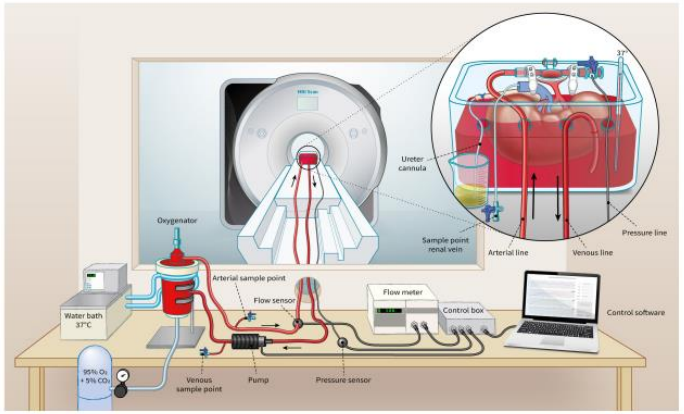
Perfluorocarbon solutions limit tubular epithelial cell injury and promote CD133+ kidney progenitor differentiation: potential use in renal assist devices for sepsis-associated acute kidney injury and multiple organ failure



Cantaluppi V., Marengo M, Dellepiane S, Medica D, Quercia AD, Castellano G, Gesualdo L, Camussi G, Ronco C. et al., NDT 2018

The main Kidney Ex vivo Perfusion Protocols: Keep it Cool?

	Preclinical studies	Clinical studies
Hypothermic machine perfusion (HMP)	Mechanism, metabolomics [1–3,4▪] Ex-vivo graft treatment [5,6] Stem cell therapy, gene modification [7,8] Gradual rewarming [9▪] Oxygenated machine perfusion [4▪]	Benefit of HMP on different donor types [10–15] -Optimization of pumping time, reconditioning, or continuous perfusion [16–18,19▪] Assessment, biomarkers [11,20–22] Ex-vivo graft treatment [23]
Normothermic machine perfusion (NMP)	Development of prolonged normothermic perfusion [25▪,26▪▪,27,28▪,29] Optimization, ex-vivo treatment [31–34,43] Assessment [28▪] Comparison of normothermic and hypothermic machine perfusion [4▪,35]	First clinical experiences [36–41] Assessment [38,39]

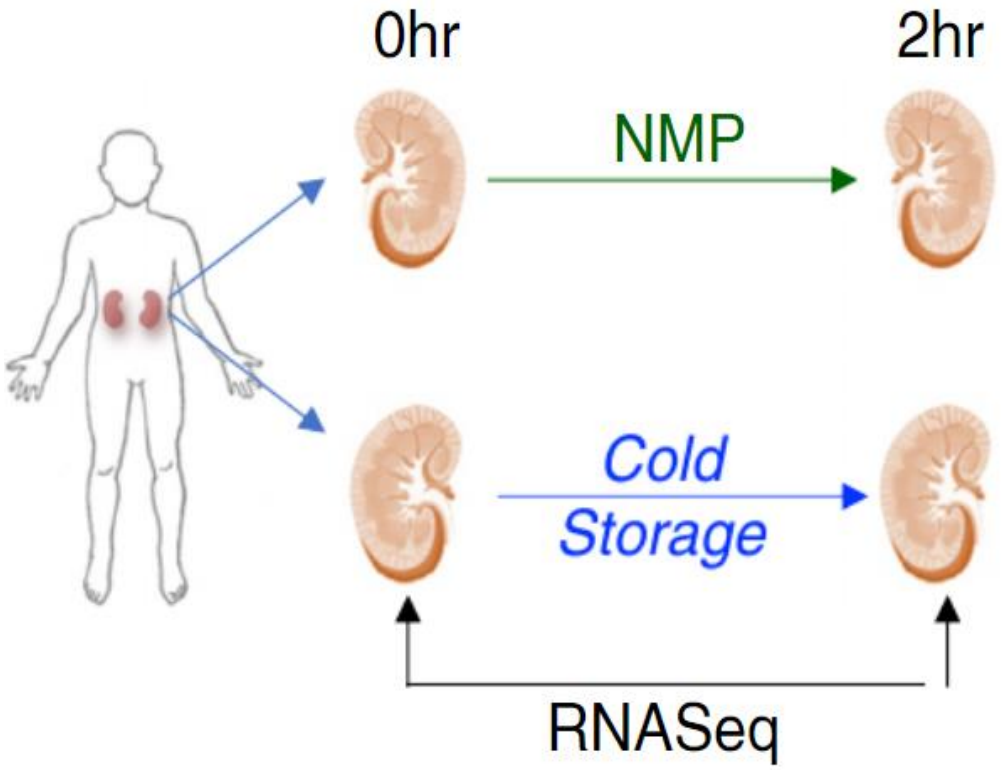


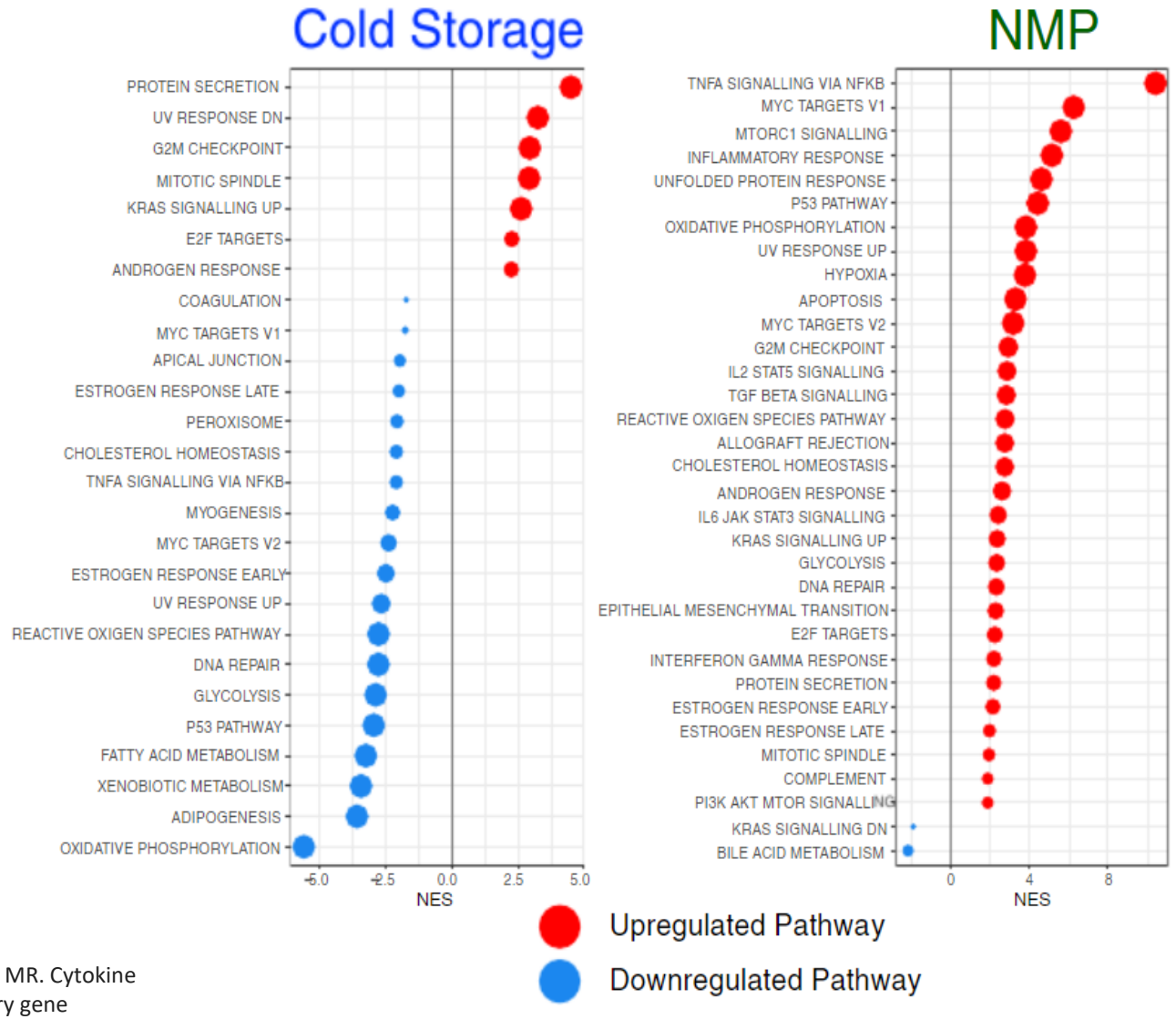
Schutter R, van Varsseveld OC, Lantinga VA, Pool MBF, Hamelink TH, Potze JH, et al. Magnetic resonance imaging during warm ex vivo kidney perfusion. Artif. Organs. 2022;00:1–12. https://doi.org/10.1111/ aor.14391

Curr Opin Organ Transplant. 2018 Jun;23(3):369-374.

Cold Storage vs. Normothermic Machine Perfusion

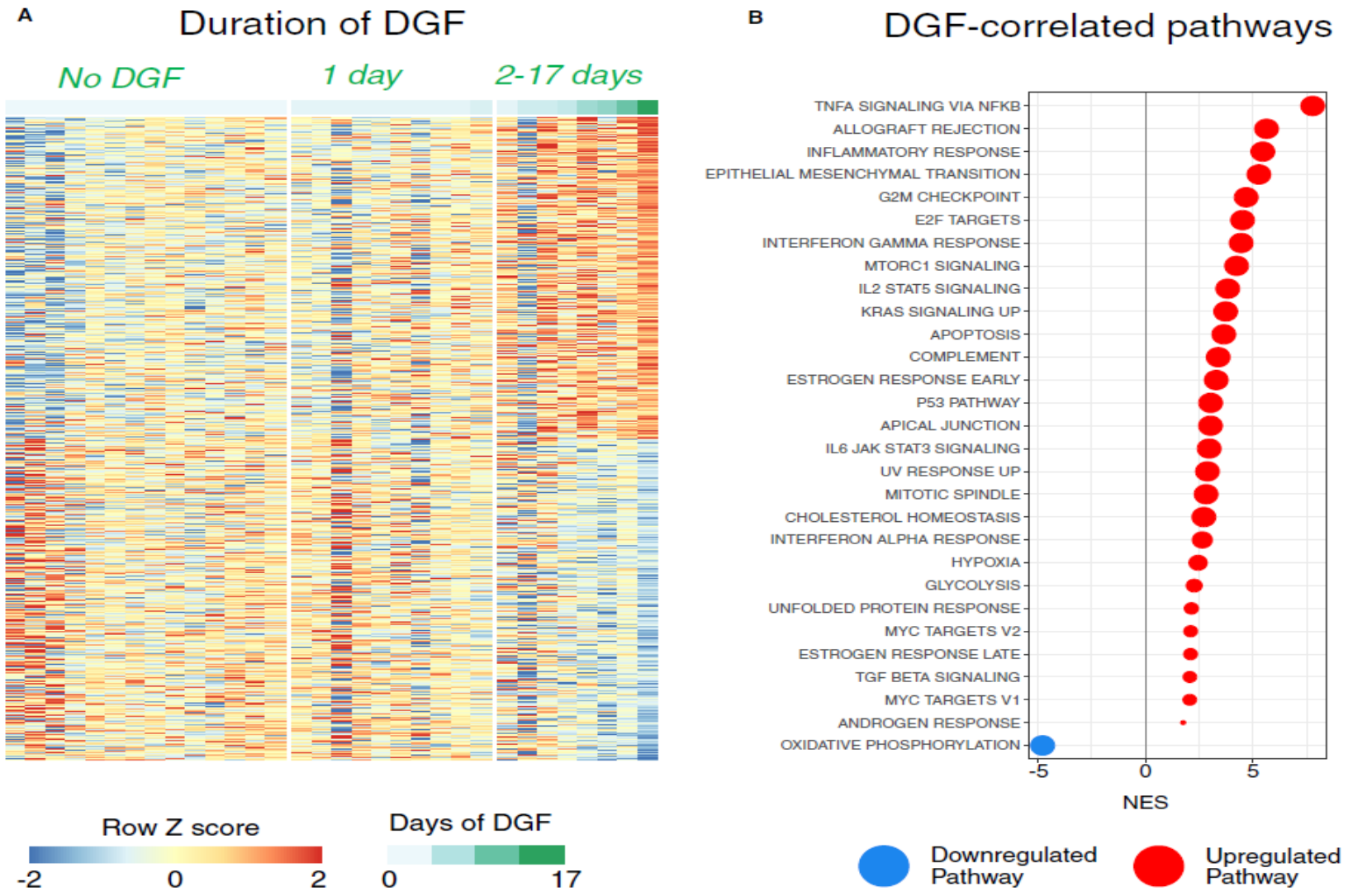
5 pairs of kidneys per group





Ferdinand JR, Hosgood SA, Moore T, Ferro A, Ward CJ, Castro-Dopico T, Nicholson ML, Clatworthy MR. Cytokine absorption during human kidney perfusion reduces delayed graft function-associated inflammatory gene signature. Am J Transplant. 2021 Jun;21(6):2188-2199.

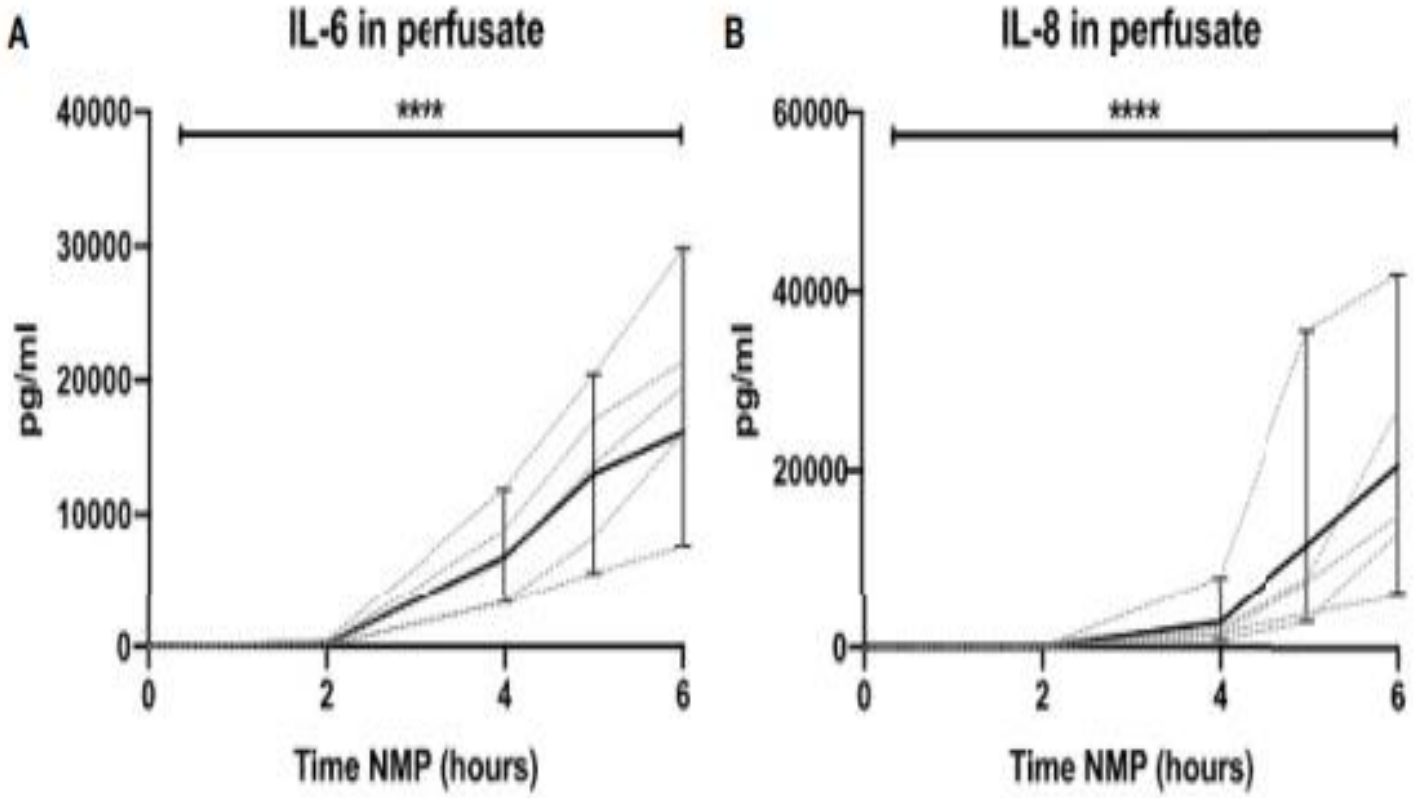
Delayed Graft Function (DGF)



Correlation between inflammatory pathways genes and TNF-alpha/NF-kB signalling and DGF.

Ferdinand JR, Hosgood SA, Moore T, Ferro A, Ward CJ, Castro-Dopico T, Nicholson ML, Clatworthy MR. Cytokine absorption during human kidney perfusion reduces delayed graft function-associated inflammatory gene signature. Am J Transplant. 2021 Jun;21(6):2188-2199.

High Levels of Pro-Inflammatory Cytokines Are Released Normothermic Machine Perfusion



Pro-inflammatory Cytokines' can be a target for therapy delivery.

Jager NM, Venema LH, Arykbaeva AS, Meter-Arkema AH, Ottens PJ, van Kooten C, Mollnes TE, Alwayn IPJ, Leuvenink HGD, Pischke SE and PROPER study consortium (2022) Complement is Activated During Normothermic Machine Perfusion of Porcine and Human Discarded Kidneys. Front. Immunol. 13:831371. doi: 10.3389/fimmu.2022.831371

Different cytokine and immune cell patterns can offer an important target to investigate for therapeutic interventions.

	Kidneys with urine recirculation ($n = 8$)		Kidneys without urine recirculation ($n = 4$)		p-value*** 1 h	p-value*** 6 h
	1 h**	6 h**	1 h**	6 h**		
GM-CSF	420.6, 9,993	53.5, 2,300	10,000, 0	12.6, 27.7	0.11	0.21
IFN-γ	10,000, 0	10,000, 9,982	10,000, 0	10,000, 0	>0.9	0.42
IL-10	2,160, 8196	1,890, 3,727	5,023, 9,988	1,214, 3,607	>0.9	>0.9
IL-12p40	10,000, 0	10,000, 7,481	10,000, 0	10,000, 7,499	>0.9	0.83
IL-12p70	10,000, 0	10,000, 0	10,000, 0	10,000, 7,493	>0.9	>0.9
IL-1RA	1,214, 2,229	1,933, 2,710	453.7, 419.7	192.6, 969	0.68	0.26
IL-1α	10,000, 0	10,000, 9,935	5,010, 9,986	10,000, 0	0.09	0.42
IL-1β	5,082, 9,986	113.7, 7,534	10,000, 7,499	1.2, 3	0.67	0.02
IL-2	10,000, 9,998	19.7, 7,518	10,000, 0	5,001, 9,999	0.42	0.53
IL-4	10,000, 0	10,000, 0	10,000, 0	10,000, 0	>0.9	>0.9
IL-6	4,493, 9,040	8,496, 4,829	19.6, 47.7	5,224, 14,384	0.11	0.68
IL-8	66.1, 10,943	16,501, 35,438	23.9, 55.5	17,625, 9,744	0.77	0.89
TNF-α	18.4, 560.8	459.7, 1,277	8.9, 9.4	354.7, 221.3	0.46	0.37

Number of cells in pg/ml; overall perfusate volume = 500 ml.

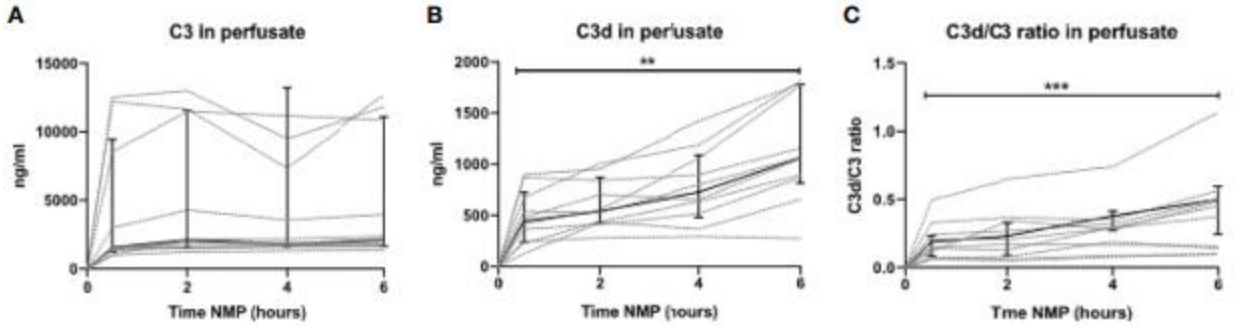
**Time after start of NMP, values in median and IQR (interquartile range).*

***P-value result of comparison with and without urine recirculation.*

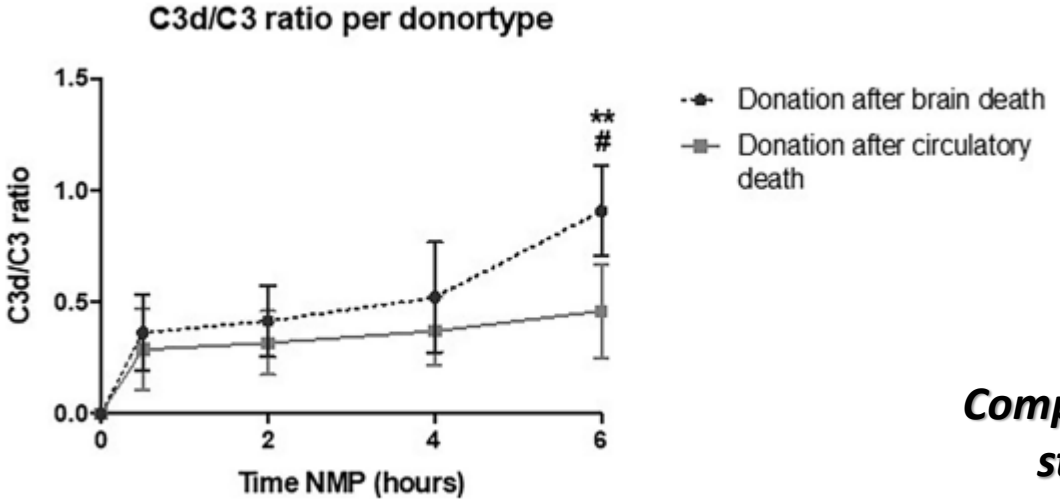
GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

IL-1β was higher in perfusates with higher content of NGAL.
Higher NGAL perfusates have higher GM-CSF.
Arterial Flow was higher in kidneys with lower TNFα.

Normothermic kidney machine perfusion induces complement activation



Perfusate C3d/C3 ratio of human kidneys retrieved from brain-dead donors is significantly higher after 6 h of normothermic machine perfusion.



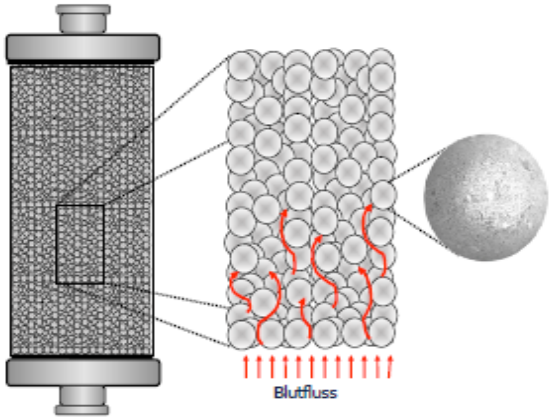
Kidneys retrieved from brain-dead donors showed significantly higher C3d/C3 ratio after 6 h of normothermic machine perfusion than kidneys retrieved after circulatory death.

Complement inhibition during NMP might thus be a promising strategy to reduce renal injury and improve renal graft function prior to transplantation

Jager NM, Venema LH, Arykbaeva AS, Meter-Arkema AH, Ottens PJ, van Kooten C, Mollnes TE, Alwayn IPJ, Leuvenink HGD, Pischke SE and PROPER study consortium (2022) Complement is Activated During Normothermic Machine Perfusion of Porcine and Human Discarded Kidneys. Front. Immunol. 13:831371. doi: 10.3389/fimmu.2022.831371

Adsorption to Modulate the Inflammatory Response

Polymer-Technology

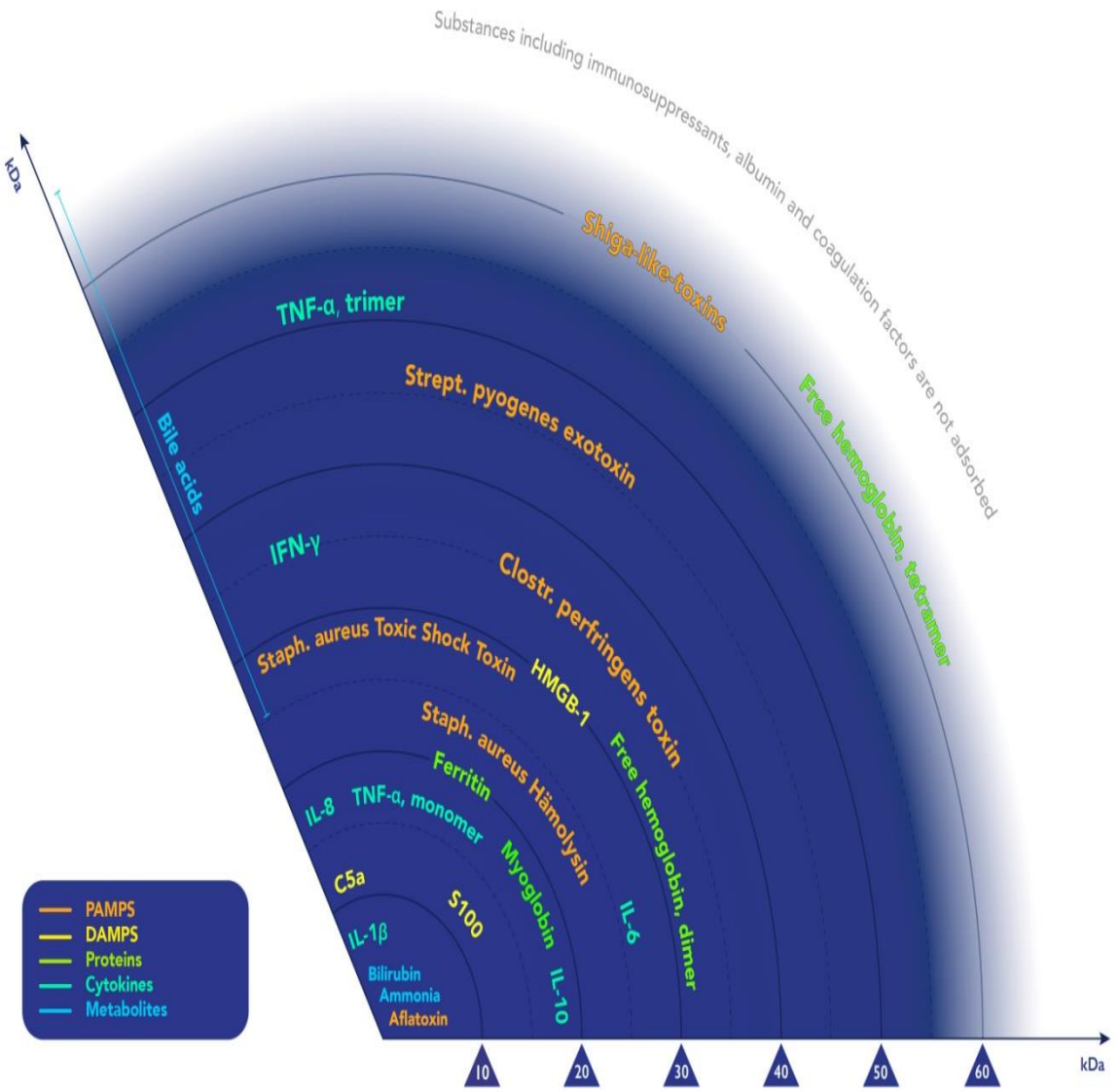


- 300ml filter with a „bead"-design
- Hightech-polymer
- Size selection < 55kD
- Low flow resistance
- 120ml bloodvolume / filling volume
- Pre-filled with sodium-chlorid
- Gamma-steril, 3 year storage

PAMPs (Pathogen Associated Molecular Patterns)

DAMPs (Damage Associated Molecular Patterns): Complement Factors C3a, C5a, inflammatory cytokines

CytoSorb adsorption spectrum

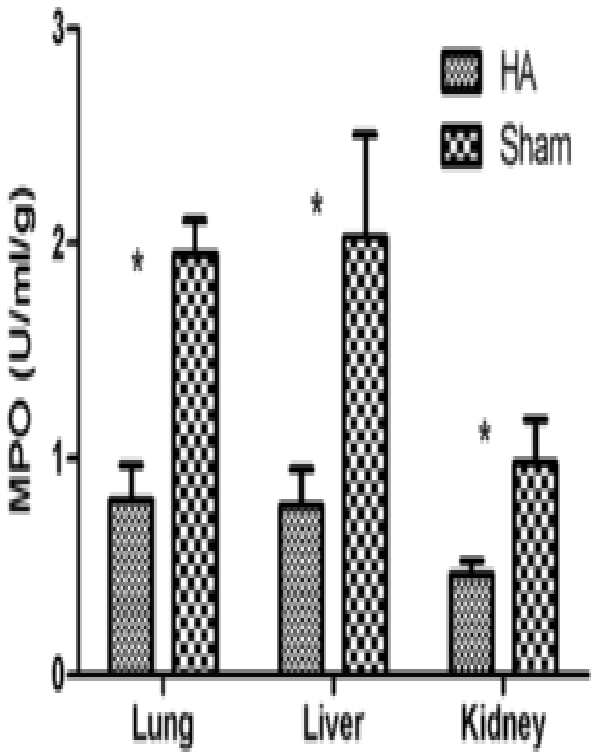


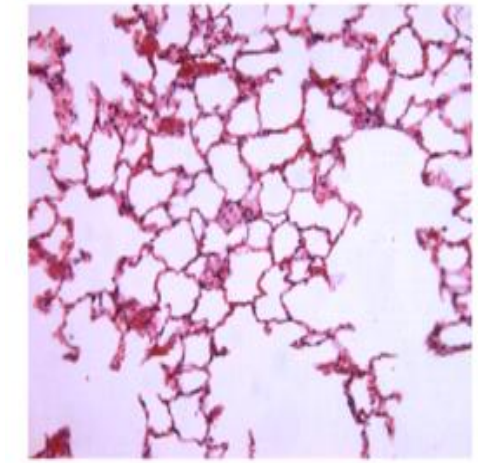
Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

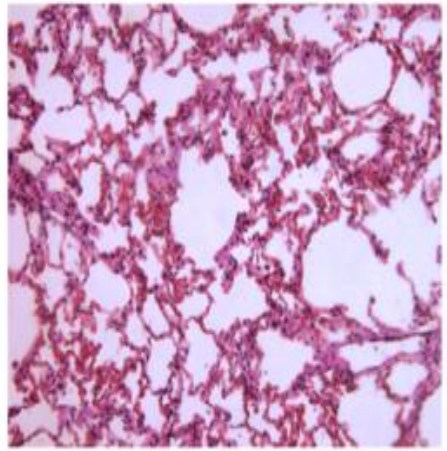
Zhi-Yong Peng[1,2], Jeffery V Bishop[2], Xiao-Yan Wen[1,2], Michele M Elder[1,2], Feihu Zhou[1,2], Anan Chuasuwan[1,2], Melinda J Carter[2], Jason E Devlin[3], A Murat Kaynar[1,2], Kai Singbartl[1,2], Francis Pike[1,2], Robert S Parker[1,2,5,6], Gilles Clermont[1,2,5,6], William J Federspiel[1,2,4,6] and John A Kellum[1,2,4,6,7*]

CRITICAL CARE

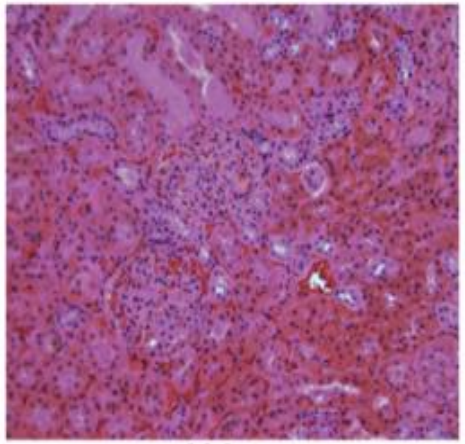
Effects of apheresis on the bacterial clearance, neutrophil infiltration, and histopathology



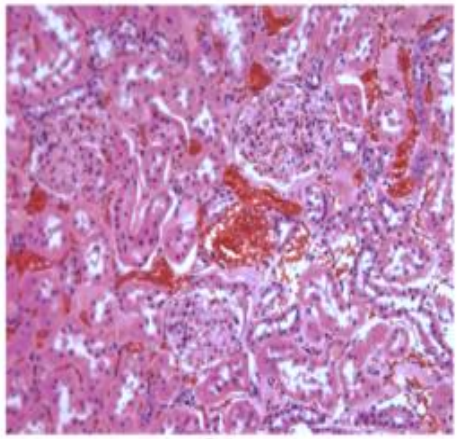




C: lung



HA



Sham

E: kidney

Animals treated with apheresis also exhibited significantly attenuated MPO activity in the lungs and kidney

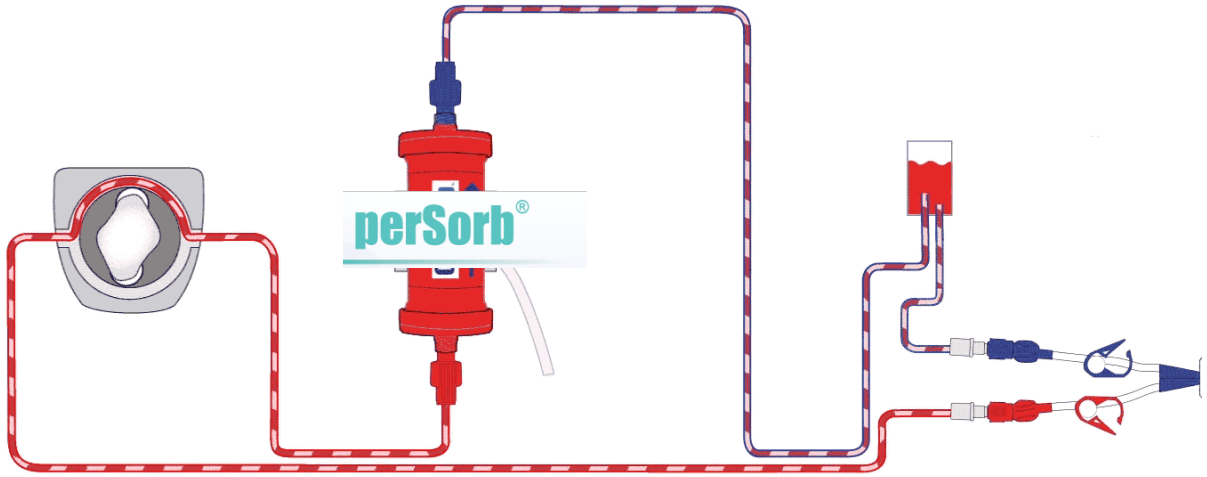
The severity of histopathology (lung, liver, and kidney), although mild overall, was consistent with the MPO results

Ischemia-reperfusion Kidney injury.....

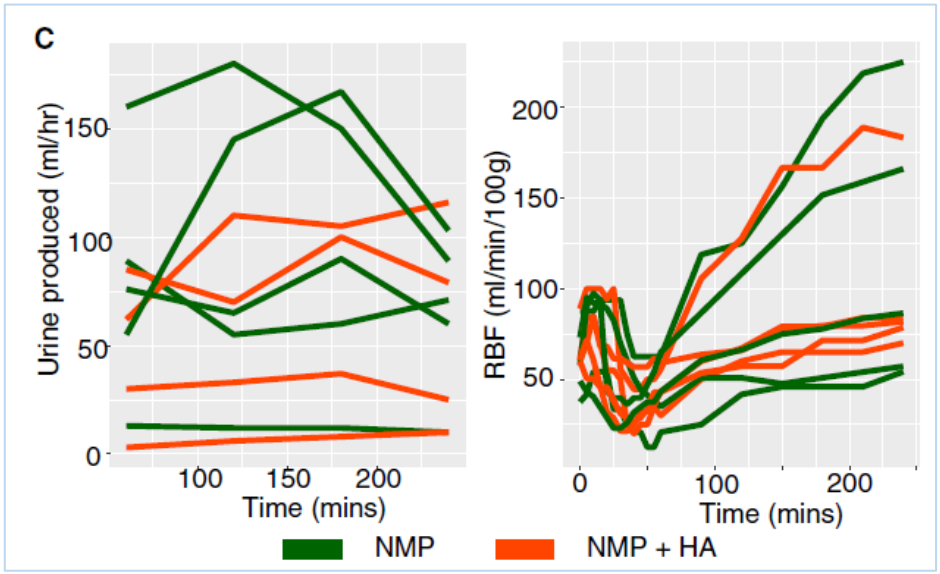
Removal of inflammatory mediators: a new opportunity?

Control of inflammatory mediators to reduce organ damage

Perfusion liquid Purification
Adsorption of toxic molecules and inflammatory mediators



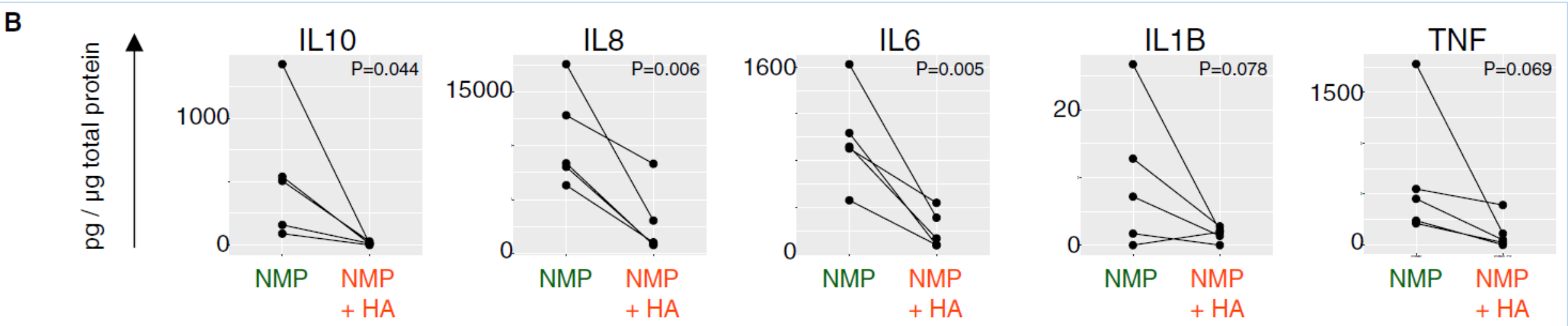
Addition of CytoSorb to reduce inflammatory mediators



During NMP the organ releases pro-inflammatory mediators that recirculate and stimulate further exacerbation of inflammation.

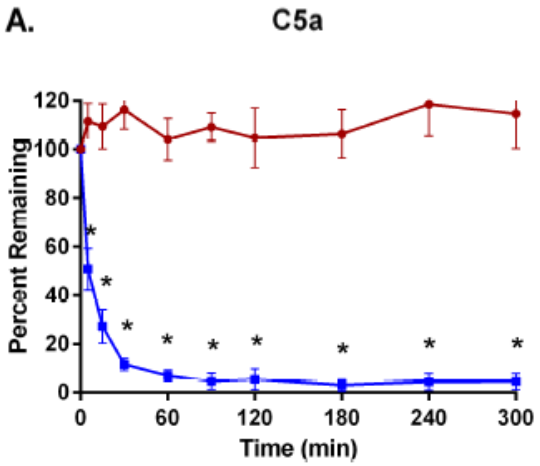
This inflammation could be improved with adsorption systems.

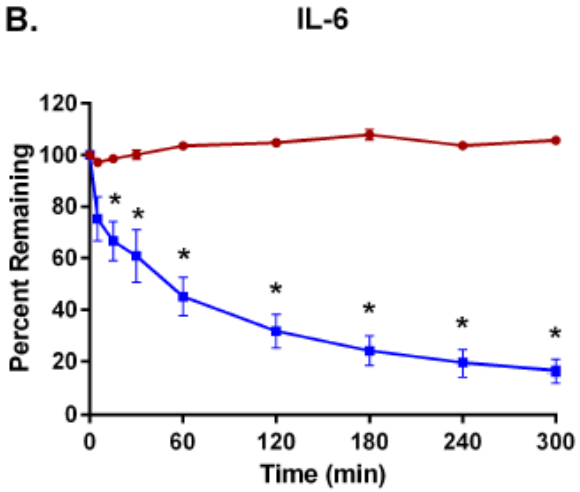
CytoSorb does not change perfusion parameters (flux and urine output), but attenuates inflammatory gene expression and has potentially clinically important effects in reducing the expression of a DGF-associated gene signature

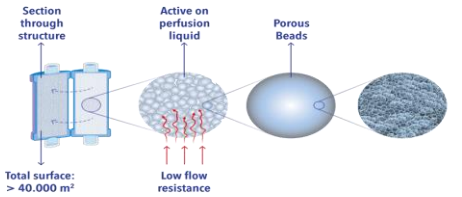


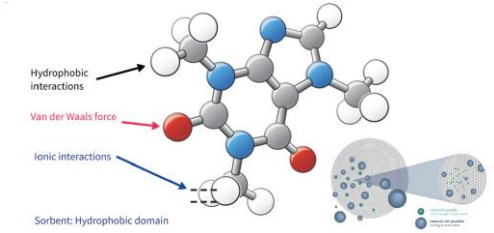
Ferdinand JR, Hosgood SA, Moore T, et al. Cytokine absorption during human kidney perfusion reduces delayed graft function-associated inflammatory gene signature. *Am J Transplant*. 2021;21(6):2188-2199.

Perfusion liquid purification in kidney ex vivo perfusion can be an immunomodulatory strategy

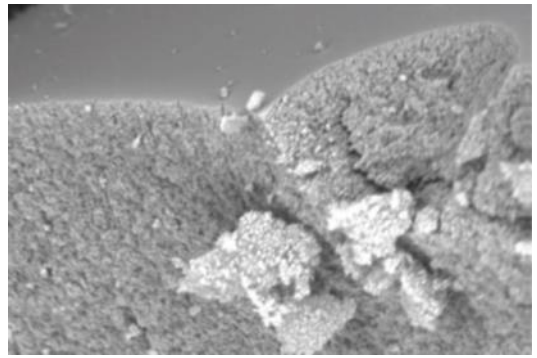






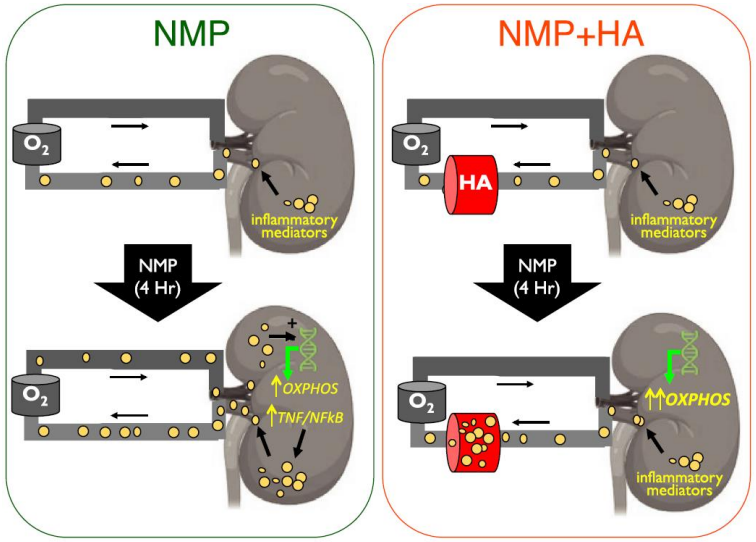


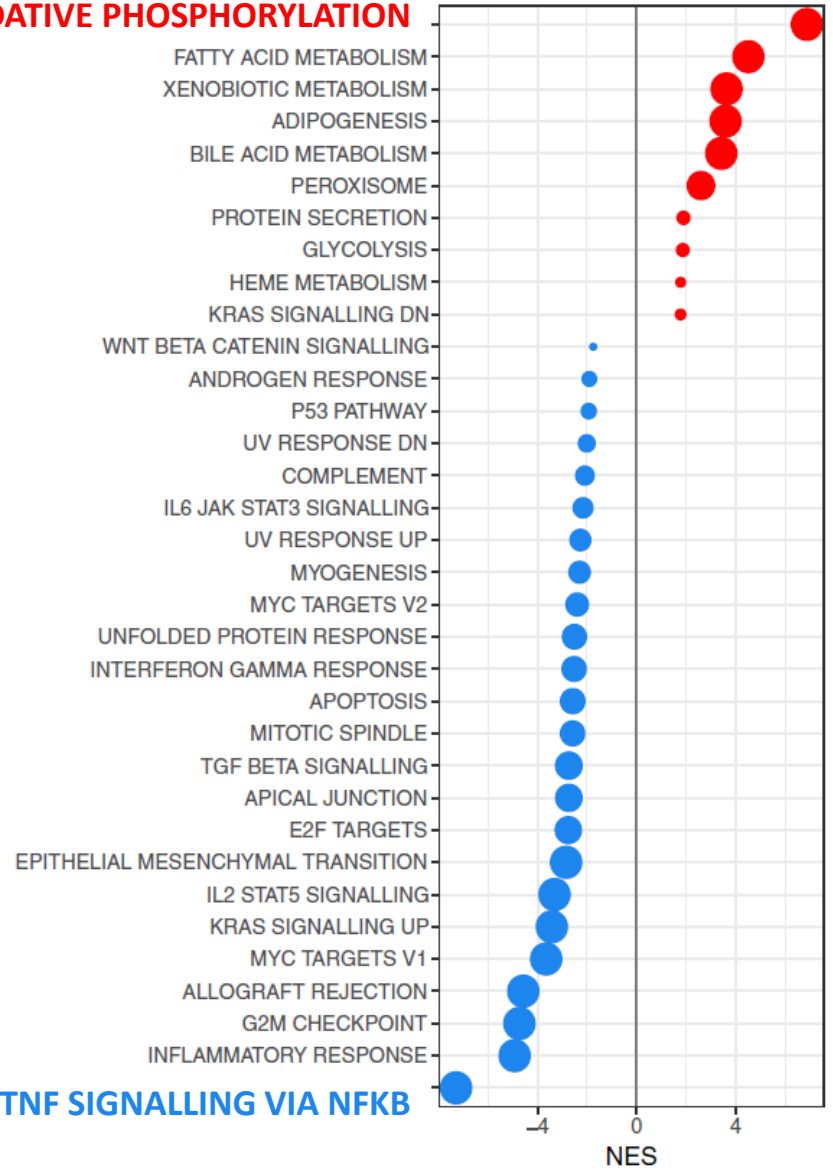
Adsorption for Complement, PAMPs and DAMPs modulation in perfusate to mitigate IRI



Gruda MC, et al. (2018) Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb sorbent porous polymer beads. PLoS ONE 13(1): e0191676.

Effects of CytoSorb on gene expression



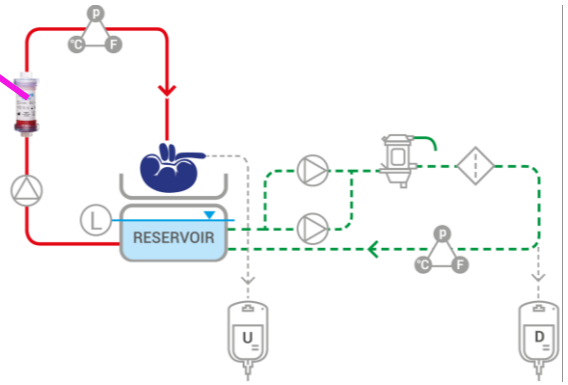


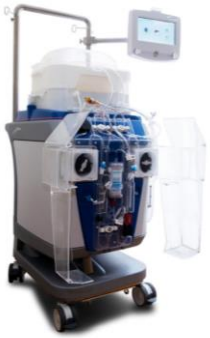
CytoSorb attenuates inflammatory gene expression and has potentially clinically important effects in reducing the expression of a DGF-associated gene signature

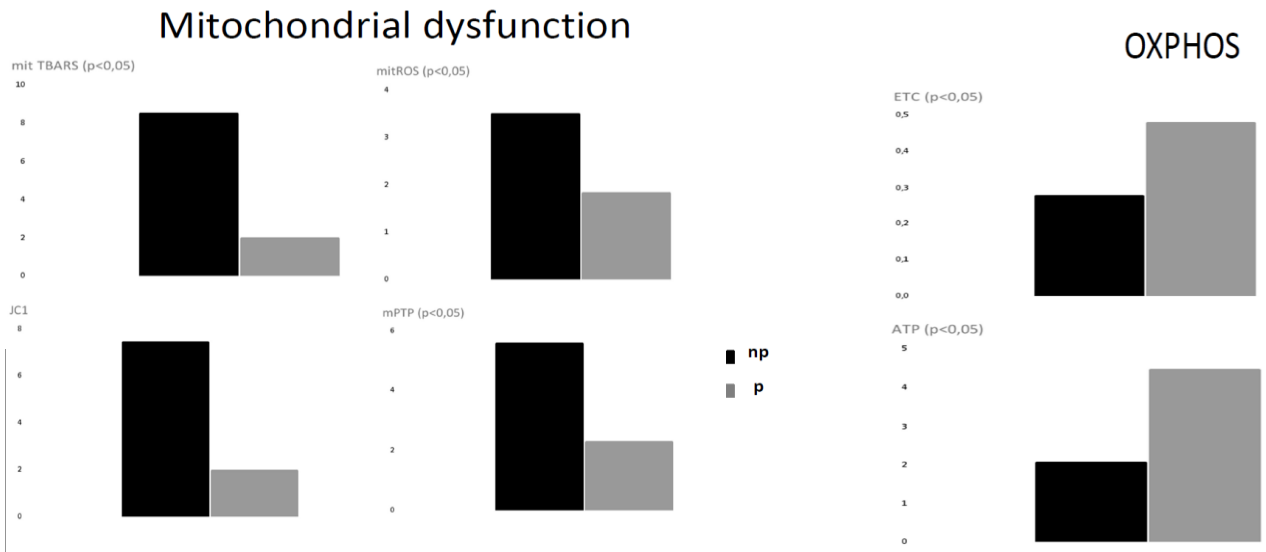
Ferdinand JR, Hosgood SA, Moore T, et al. Cytokine absorption during human kidney perfusion reduces delayed graft function-associated inflammatory gene signature. *Am J Transplant*. 2021;21(6):2188-2199.

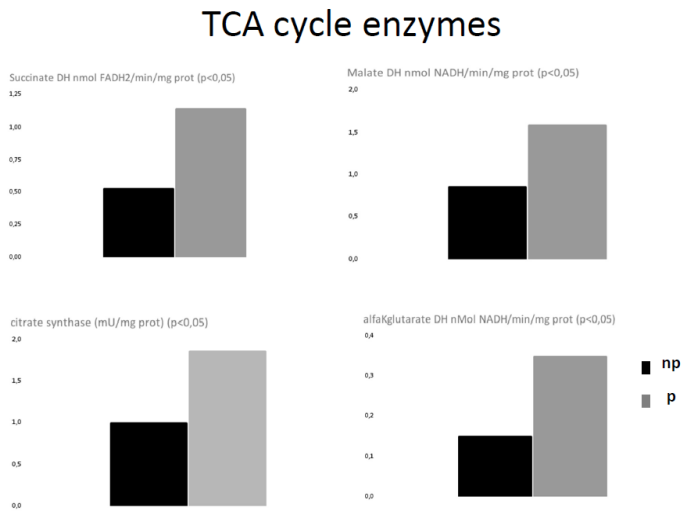
PerSorb inflammatory mediators adsorption limits IRI: pre Clincal results

PerLife + PerSorb

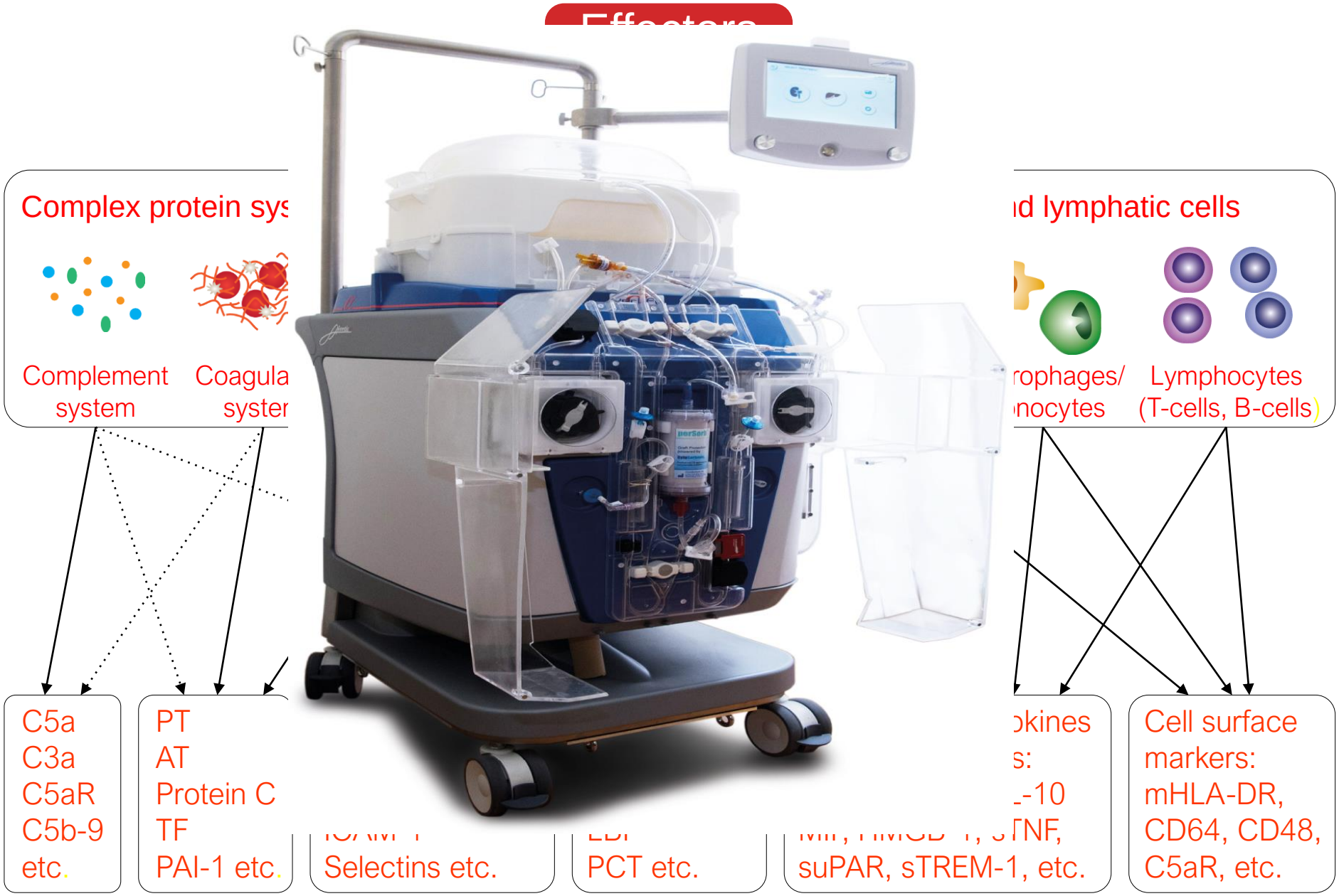








Machine Perfusion, in particular Machine perfusion integrationg PerSorb, significantly restored the homeostasis of the mitochondrial network with a possible limitation of IRI and promoting tubular regeneration.

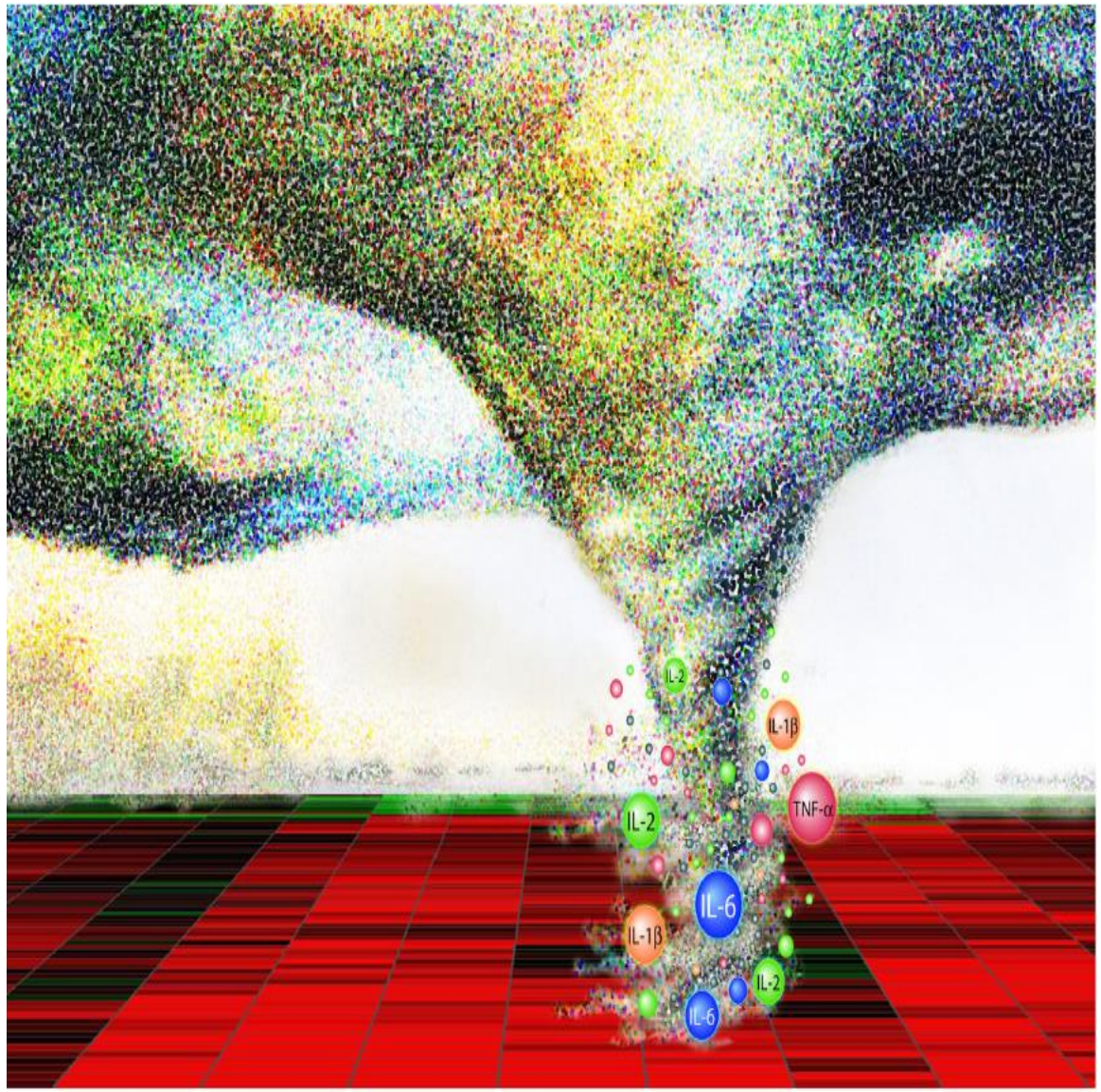


(Partly adapted from Reinhart et al. 2012)

Into the Eye of the Cytokine Storm

Jennifer R. Tisoncik,[a] Marcus J. Korth,[a] Cameron P. Simmons,[b] Jeremy Farrar,[b] Thomas R. Martin,[c] and Michael G. Katze[a]

MMBR
Journals.ASM.org



AARON CHANG
OCEAN ART
SOLANA BEACH
GALLERIES
SAN DIEGO

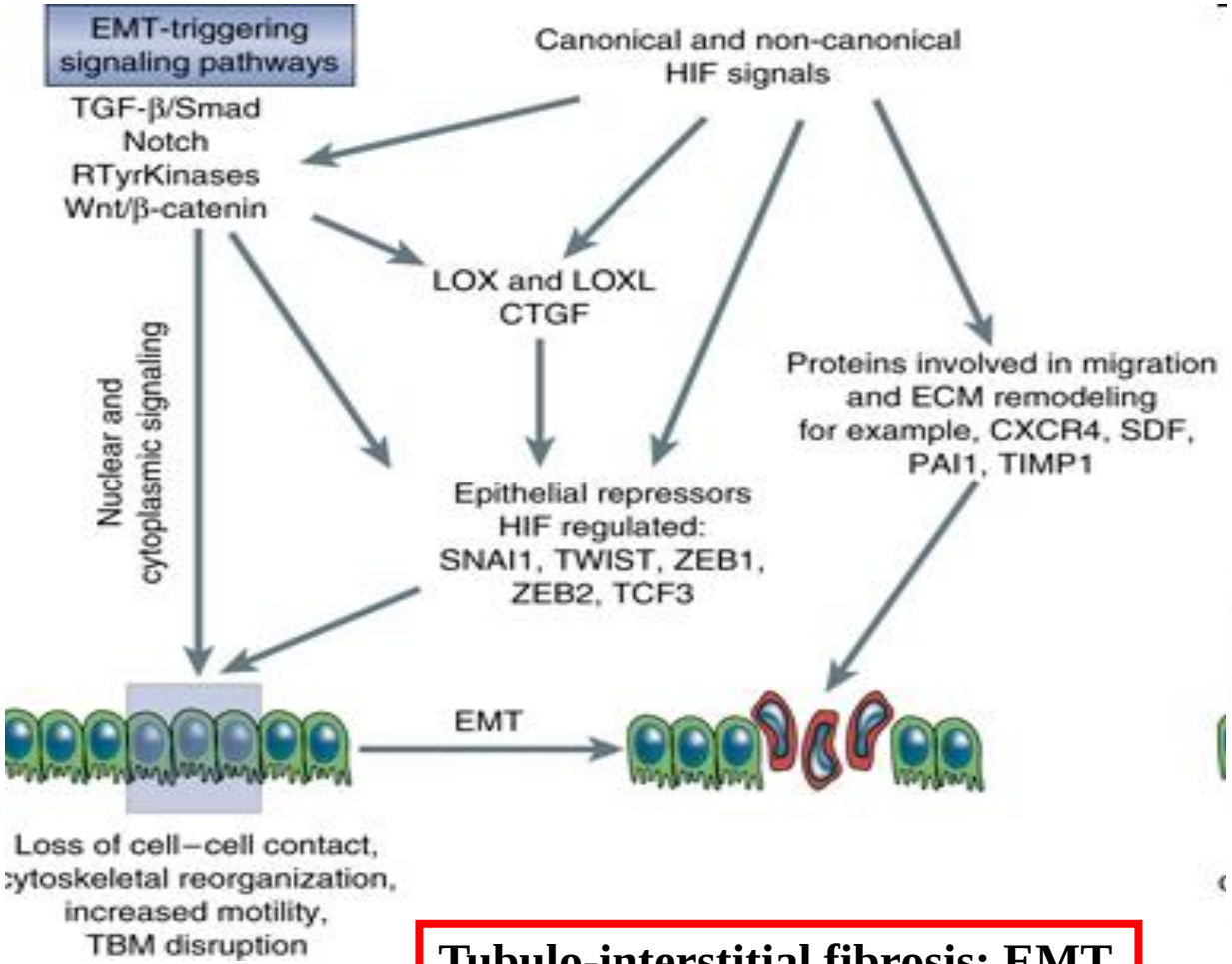
Kidney perfusion: the next future….

Courtesy by Kellum J.A.

- New biomarkers of cell injury/dysfunction
- Administration of drugs (growth factors, complement inhibitors, sIRNAs, senolytics…)
- Combination of adsorption devices and cell therapy (e.g. tubular epithelial/stem cells). Administration of stem cell-derived products such as EVs (“secretome”)

Lipocalin 2 is essential for chronic kidney disease progression in mice and humans

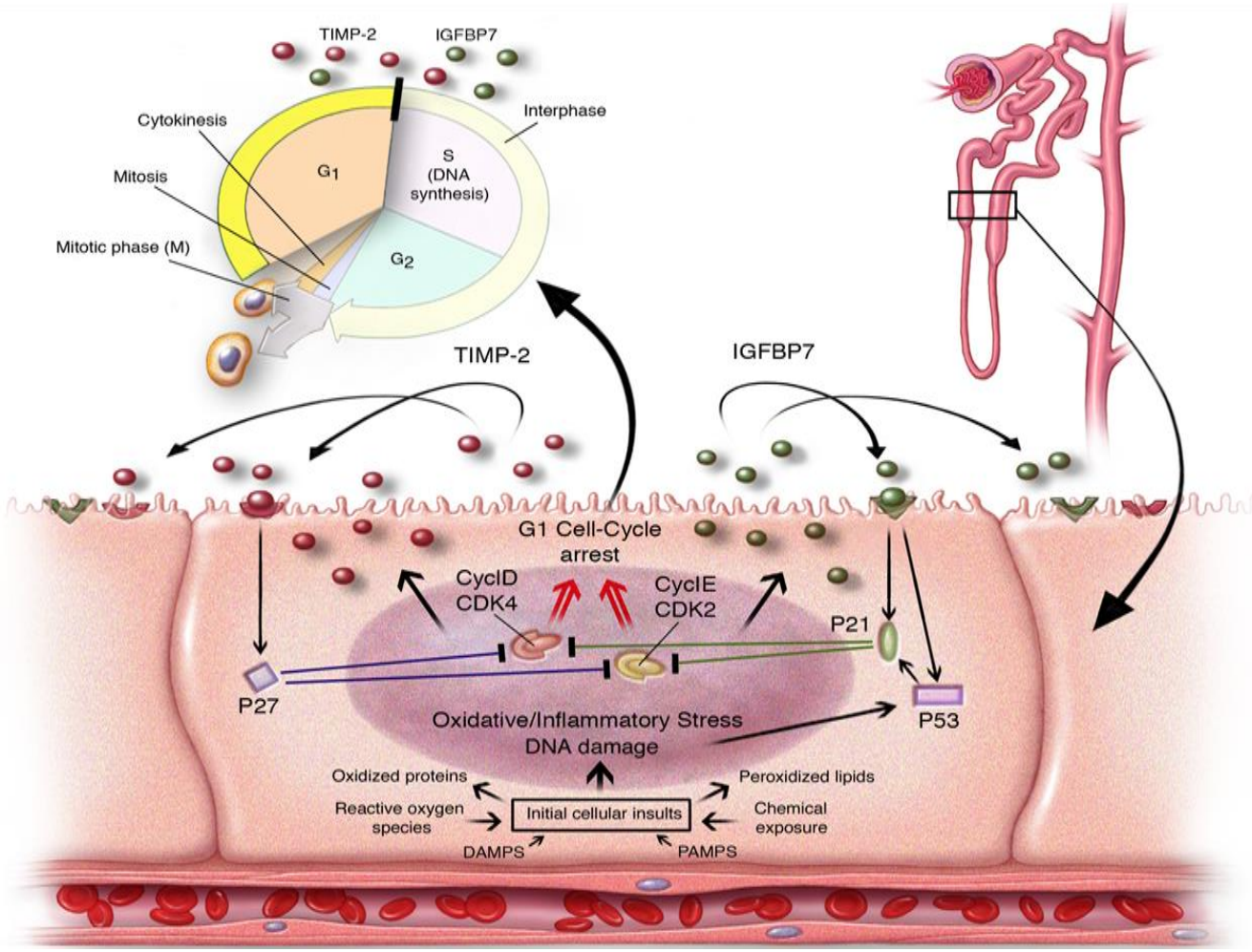
Amandine Viau,[1] Khalil El Karoui,[1] Denise Laouari,[1] Martine Burtin,[1] Clément Nguyen,[1] Kiyoshi Mori,[2] Evangéline Pillebout,[1] Thorsten Berger,[3] Tak Wah Mak,[3] Bertrand Knebelmann,[1] Gérard Friedlander,[1] Jonathan Barasch,[2] and Fabiola Terzi[1]



Tubulo-interstitial fibrosis: EMT

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kianoush Kashani[1], Ali Al-Khafaji[2], Thomas Ardiles[3], Antonio Artigas[4], Sean M Bagshaw[5], Max Bell[6], Azra Bihorac[7], Robert Birkhahn[8], Cynthia M Cely[9], Lakhmir S Chawla[10], Danielle L Davison[10], Thorsten Feldkamp[11], Lui G Forni[12], Michelle Ng Gong[13], Kyle J Gunnerson[14], Michael Haase[15], James Hackett[16], Patrick M Honore[17], Eric AJ Hoste[18], Olivier Joannes-Boyau[19], Michael Joannidis[20], Patrick Kim[21], Jay L Koyner[22], Daniel T Laskowitz[23], Matthew E Lissauer[24], Gernot Marx[25], Peter A McCullough[26], Scott Mullaney[27], Marlies Ostermann[28], Thomas Rimmelé[29], Nathan I Shapiro[30], Andrew D Shaw[31], Jing Shi[32], Amy M Sprague[33], Jean-Louis Vincent[34], Christophe Vinsonneau[35], Ludwig Wagner[36], Michael G Walker[32], R Gentry Wilkerson[37], Kai Zacharowski[38] and John A Kellum[39*]

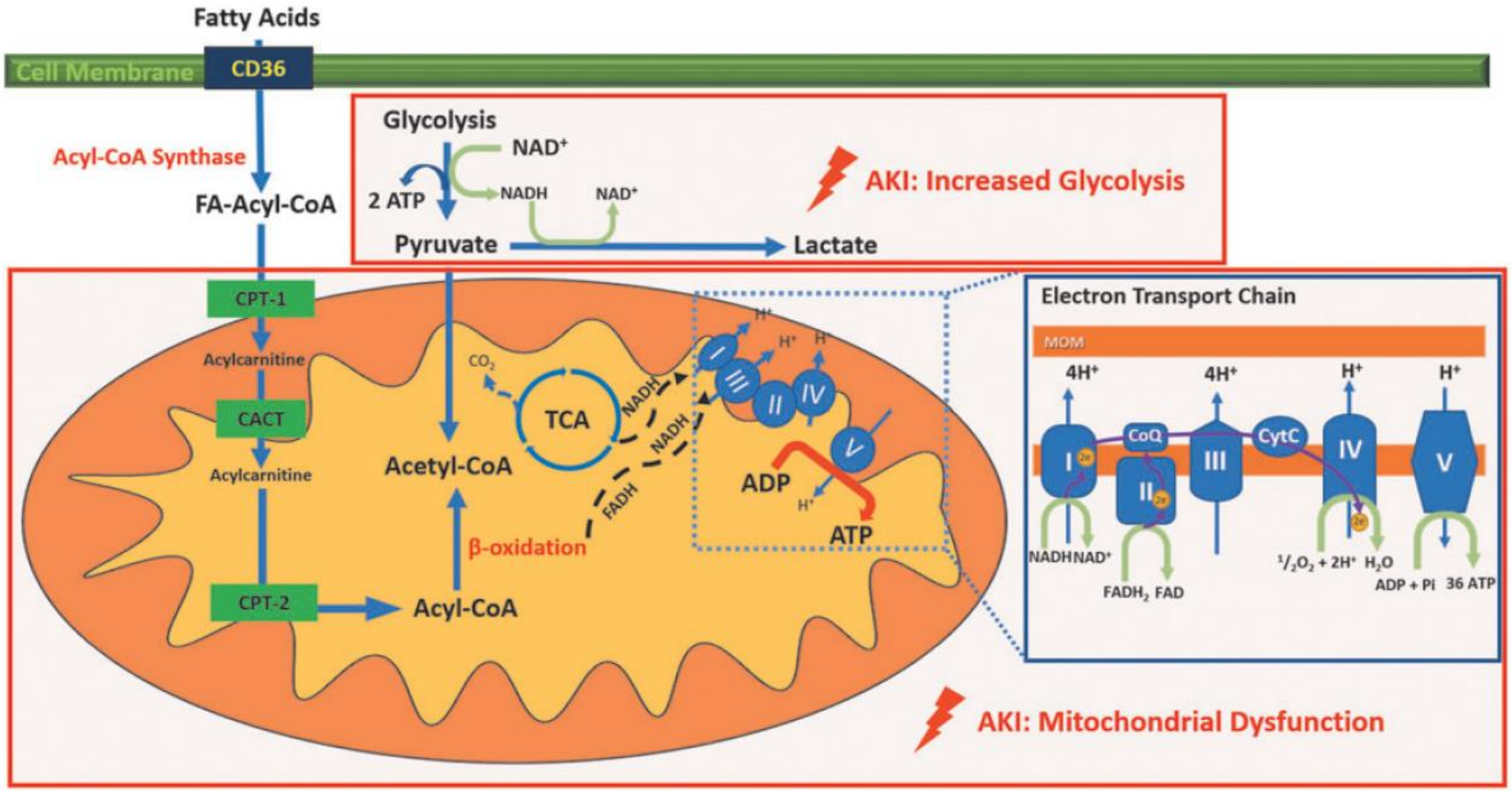


Innovations and Emerging Therapies to Combat Renal Cell Damage: NAD^+ As a Drug Target

Carlos L. Manrique-Caballero,[1,2] John A. Kellum,[1,2] Hernando Gómez,[1,2] Francesca De Franco,[3] Nicola Giacchè,[3] and Roberto Pellicciari[3]

Therapeutics

Fatty acid oxidation, electron transport chain and glycolysis



Renal function deterioration has been associated with mitochondrial dysfunction and NAD+ depletion. Therapies aiming to restore mitochondrial function and increase NAD+ availability have gained special attention in the last two decades.

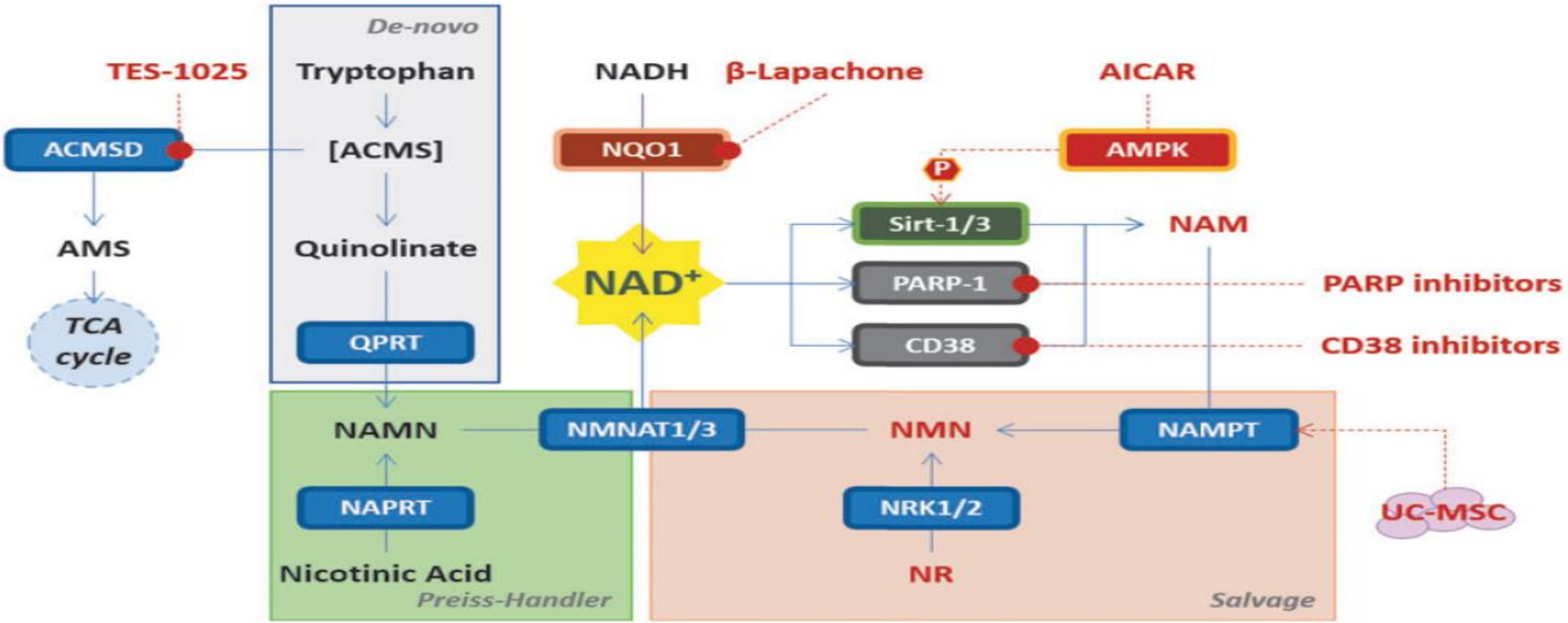
Experimental and clinical studies have shown that by restoring mitochondrial homeostasis and increasing renal tubulo-epithelial cells, NAD+ availability, AKI incidence, and chronic long-term complications are significantly decreased.

Innovations and Emerging Therapies to Combat Renal Cell Damage: NAD^+ As a Drug Target

Carlos L. Manrique-Caballero,[1,2] John A. Kellum,[1,2] Hernando Gómez,[1,2] Francesca De Franco,[3] Nicola Giacchè,[3] and Roberto Pellicciari[3]

Therapeutics

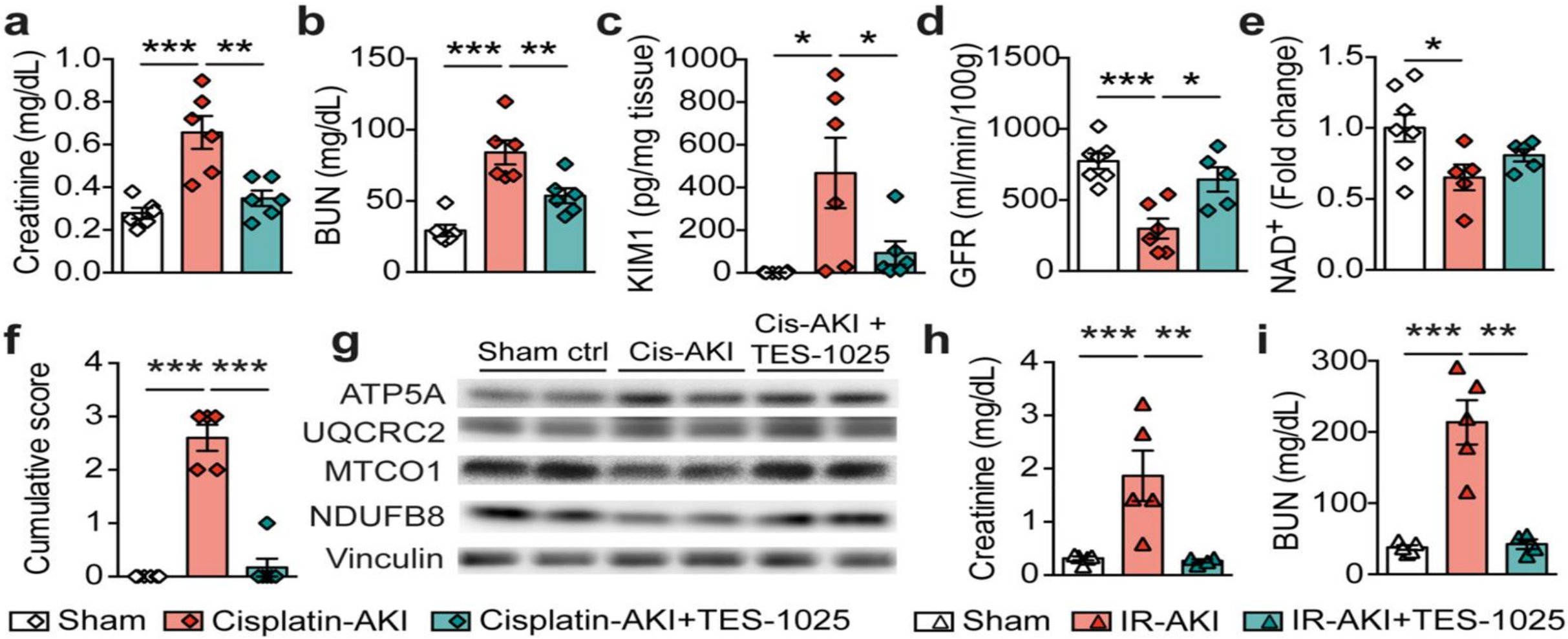
NAD+ as a drug target for AKI



De novo NAD⁺ synthesis enhances mitochondrial function and improves health

Elena Katsyuba[1], Adrienne Mottis[1], Marika Zietak[2,3], Francesca De Franco[4], Vera van der Velpen[5], Karim Gariani[1], Dongryeol Ryu[1], Lucia Cialabrini[6], Olli Matilainen[1], Paride Liscio[4],

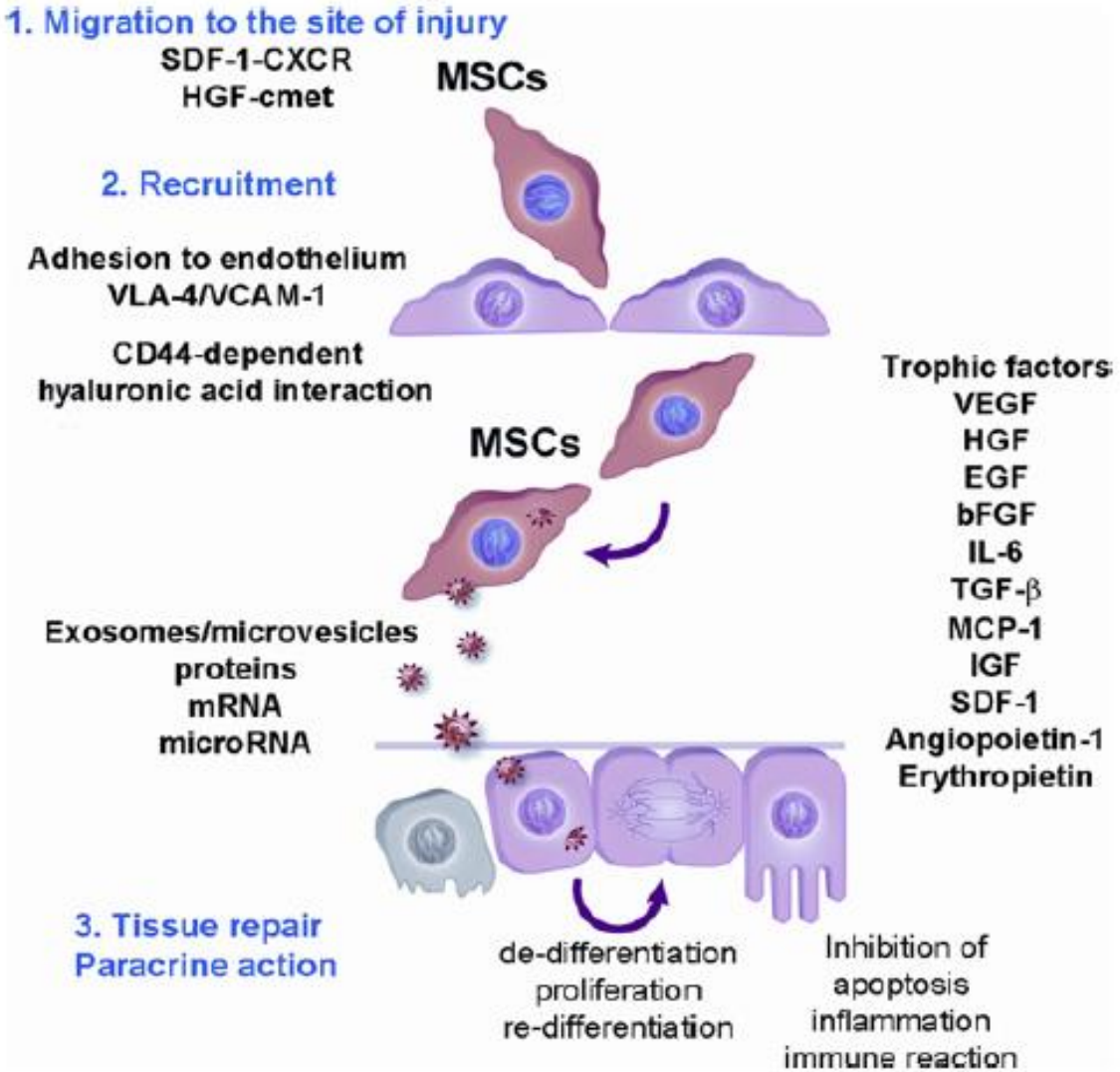
ACMSD inhibitors protect renal function in two different models of AKI

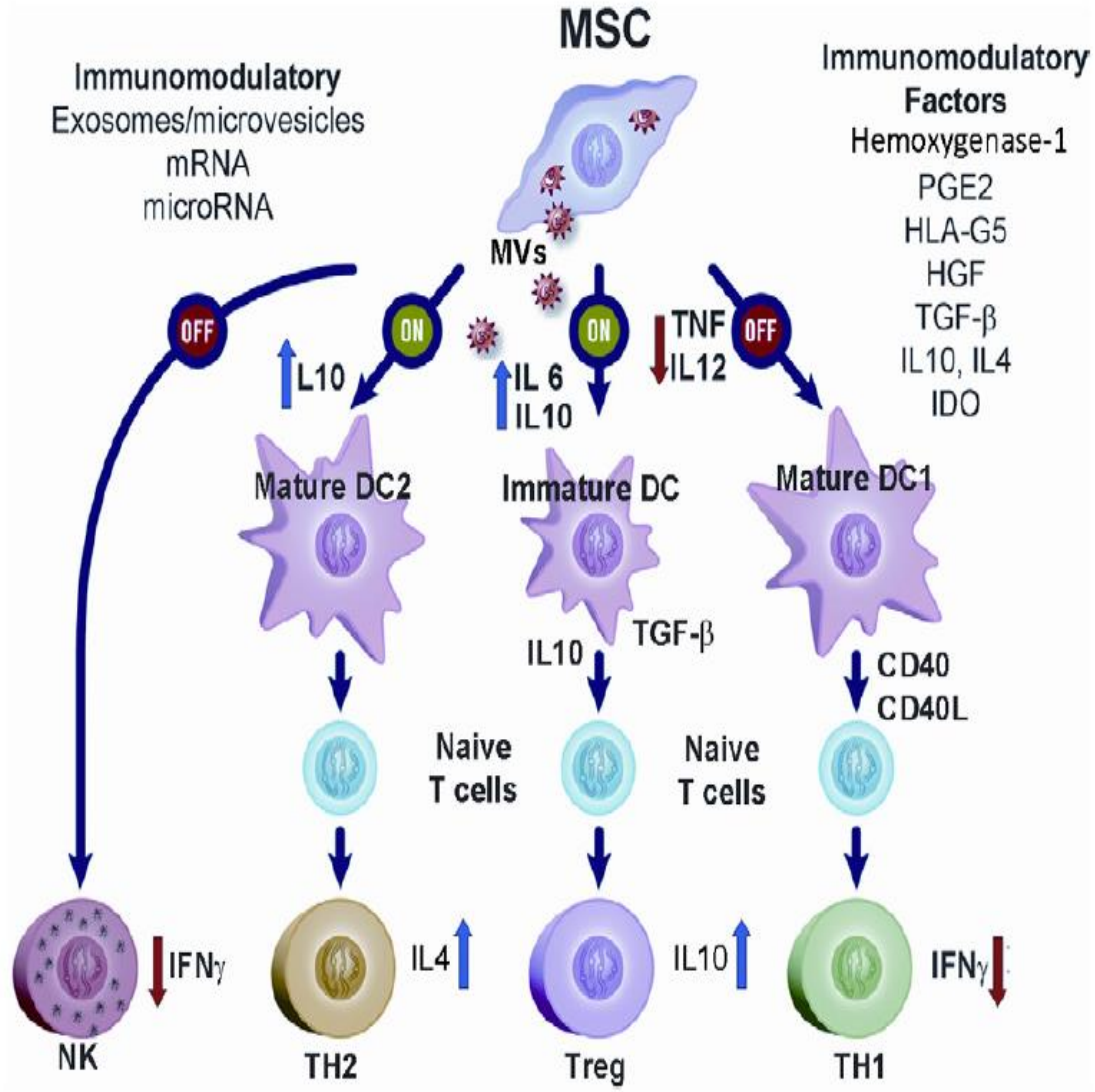


Rationale of Mesenchymal Stem Cell Therapy in Kidney Injury

Vincenzo Cantaluppi, MD, Luigi Biancone, MD, Alessandro Quercia, MD,
Maria Chiara Deregibus, MD, Giuseppe Segoloni, MD, and Giovanni Camussi, MD

AJKD

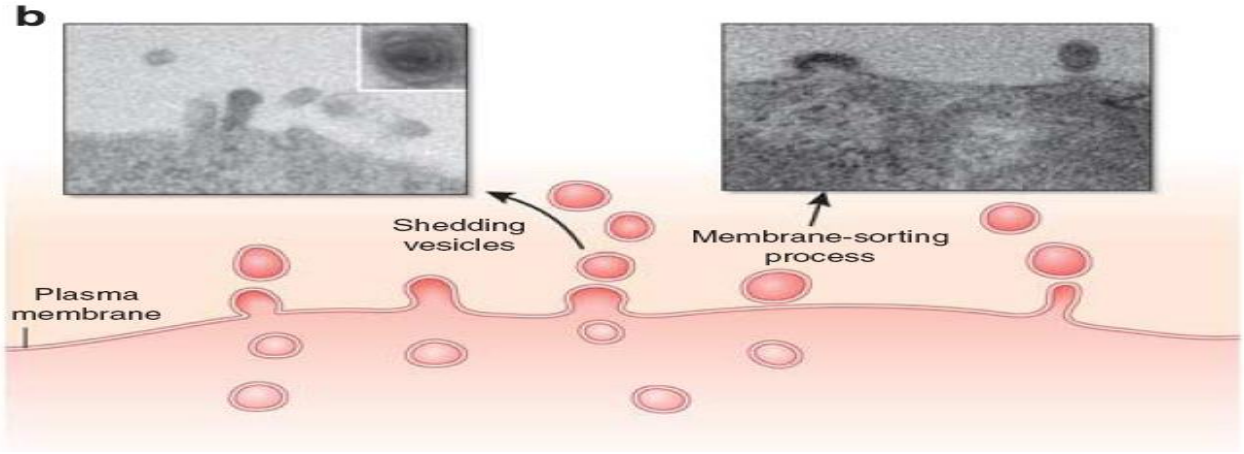


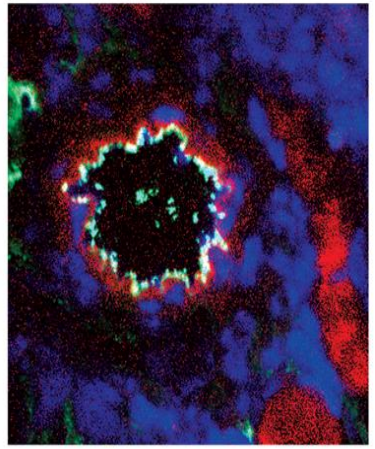


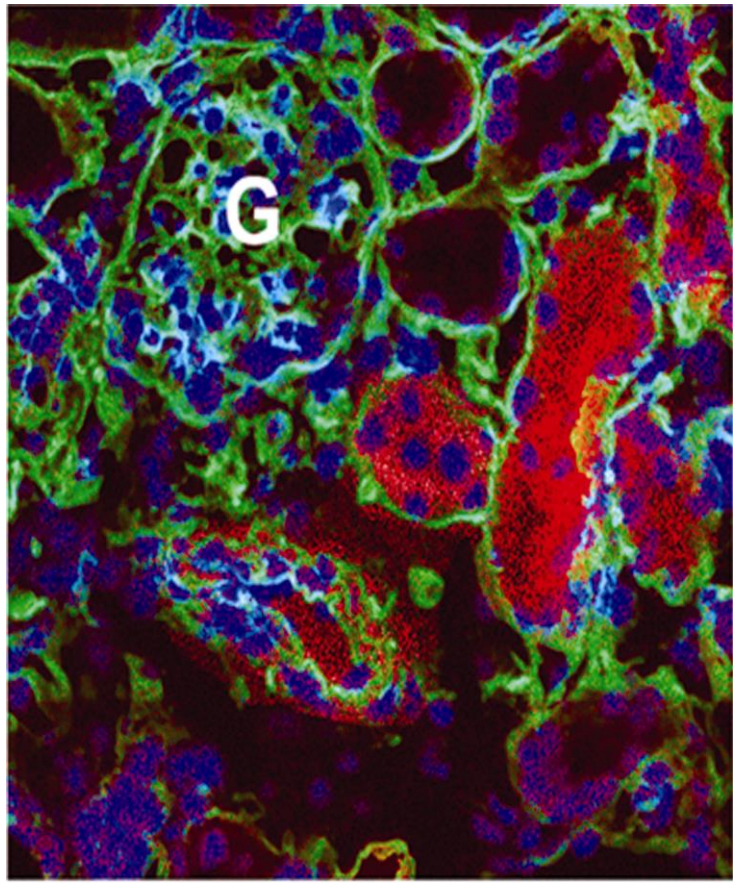
Mesenchymal Stem Cell-Derived Microvesicles Protect Against Acute Tubular Injury

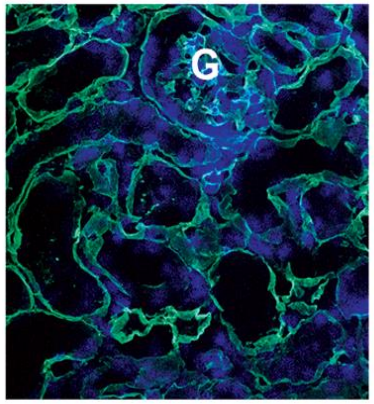
Stefania Bruno,* Cristina Grange,* Maria Chiara Deregibus,* Raffaele A. Calogero,† Silvia Saviozzi,† Federica Collino,* Laura Morando,* Alessandro Busca,‡ Michele Falda,‡ Benedetta Bussolati,* Ciro Tetta,§ and Giovanni Camussi*

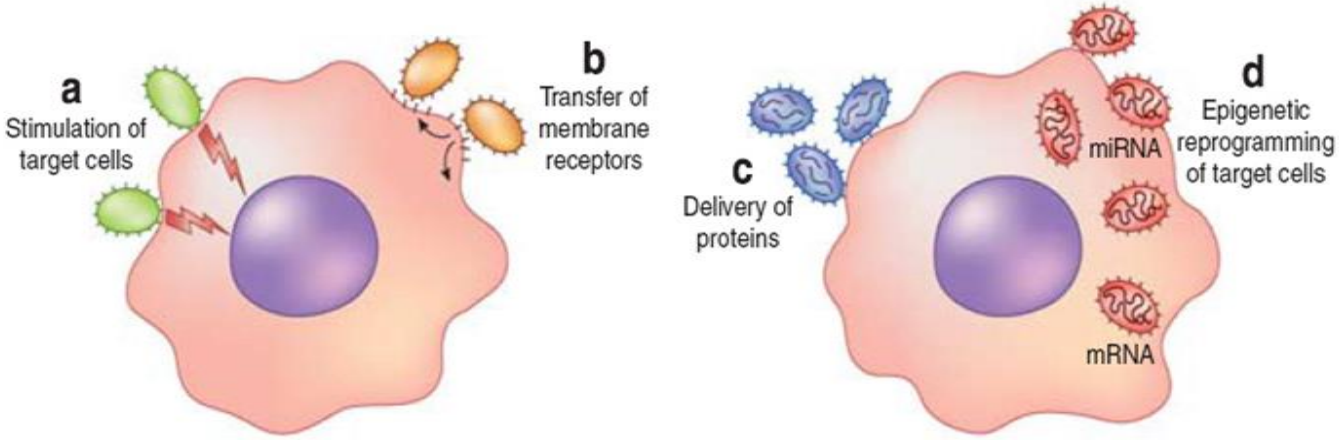
Mesenchymal Stem Cell-Derived MVs Localize within the Injured Kidney







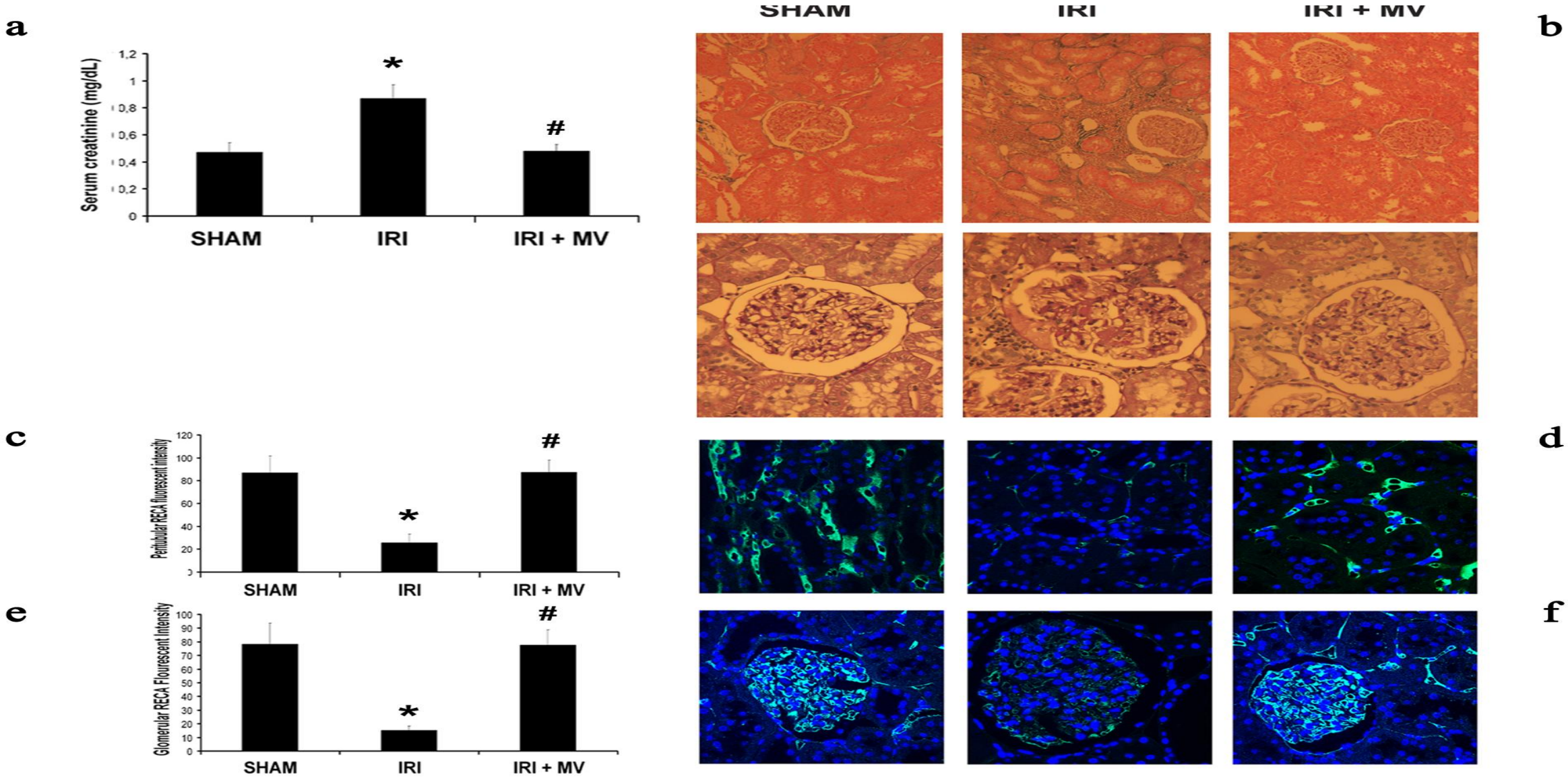




Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia–reperfusion injury by microRNA-dependent reprogramming of resident renal cells

Vincenzo Cantaluppi[1], Stefano Gatti[2], Davide Medica[1], Federico Figliolini[1], Stefania Bruno[1], Maria C. Deregibus[1], Andrea Sordi[2], Luigi Biancone[1], Ciro Tetta[3,4] and Giovanni Camussi[1]

EPC EVs inhibit capillary rarefaction and progression toward CKD



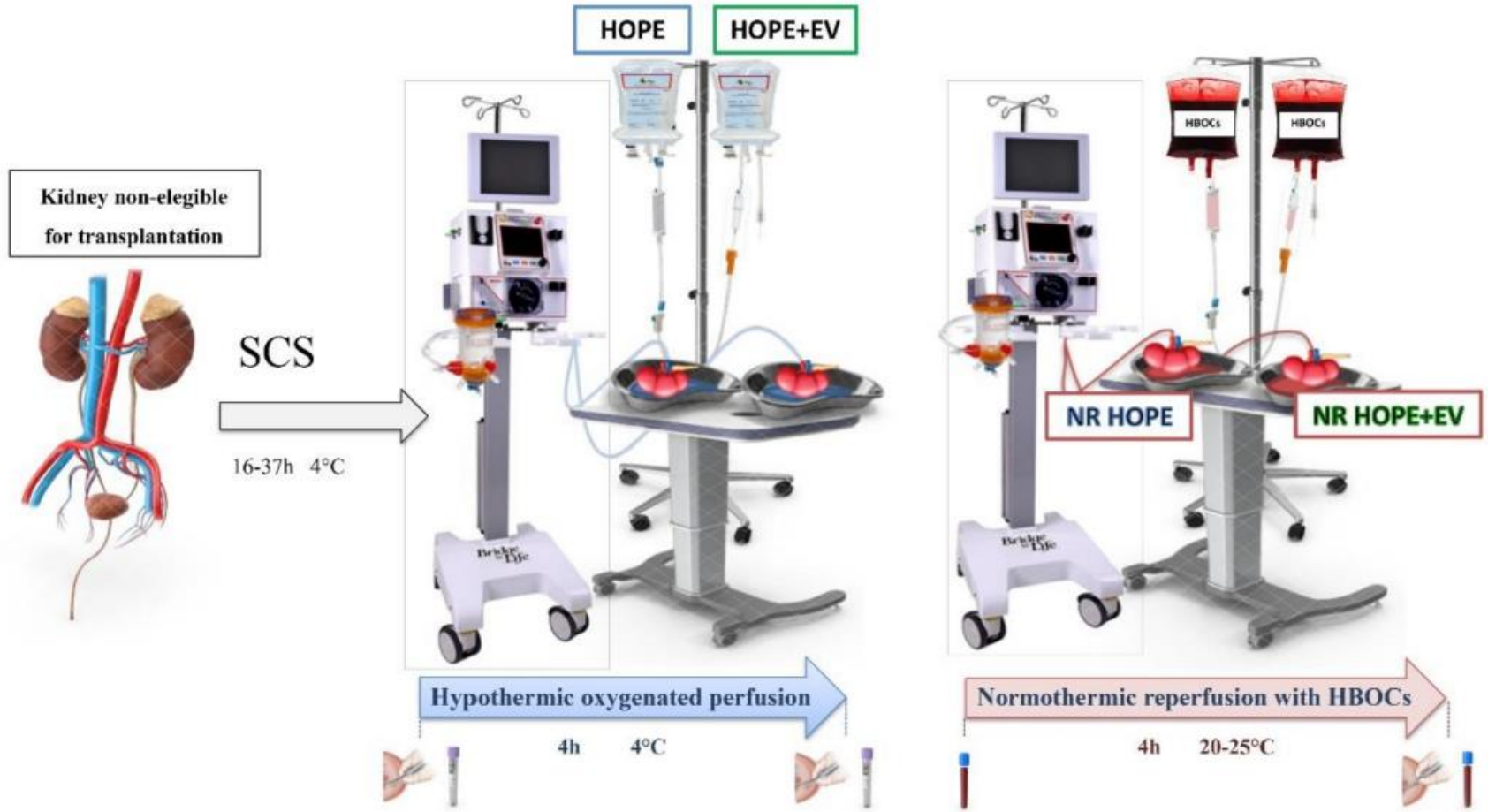
Cantaluppi V et al, Kidney Int 2012

Extracellular Vesicles Derived from Mesenchymal Stromal Cells Delivered during Hypothermic Oxygenated Machine Perfusion Repair Ischemic/Reperfusion Damage of Kidneys from Extended Criteria Donors

Teresa Rampino [1], Marilena Gregorini [1,2,*], Giuliana Germinario [3,4], Eleonora Francesca Pattonieri [1],

biology

Trial design. Samples of effluent were collected at the beginning and end of HOPE and normothermic reperfusion. Biopsies were performed at the end of hypothermic and normothermic preservations.



Explored an innovative tool for organ preservation aimed at preventing IRI damage in vulnerable marginal kidneys. EV delivery during HOPE significantly reduces IRI damage in ECD kidneys. Therefore, it can be considered a new organ preservation strategy for increasing the donor pool and improving transplant outcomes.

This is the first report on conditioning human kidneys with MSC-derived EV.

Conclusions

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- **Organ shortage** is a major challenge and several strategies have been employed to increase the number of kidneys available, including the use of **DCD donors and ECD**, both associated with **enhanced susceptibility to IRI**, **higher rates of DGF and premature graft failure**.

In the complex **pathophysiology of IRI**, inflammatory mediators (**Cytokines, Chemokines, Complement Factors**, etc) play an important role.

Therapeutic strategies for IRI limitation could be implemented also **during ex vivo perfusion.**

Among the therapeutic strategies for ex vivo perfusion, **the modulation of inflammatory mediators in the perfusate** could be a useful tool. The use of **inflammatory mediator adsorption** have shown **promising** results as an **immunomodulation strategy in ex vivo perfusion**.

- Combination of new therapeutic interventions such as **adsorption of inflammatory mediators by PerSorb, new drugs and stem cell-based therapies** should be explored in this clinical setting.

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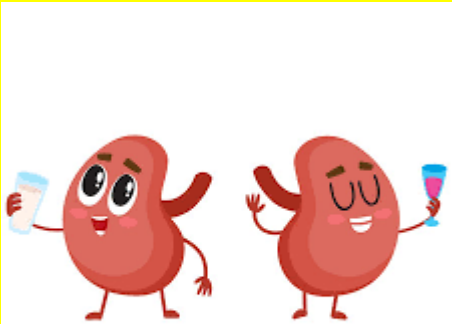
vincenzo.cantaluppi@med.uniupo.it



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