Round table

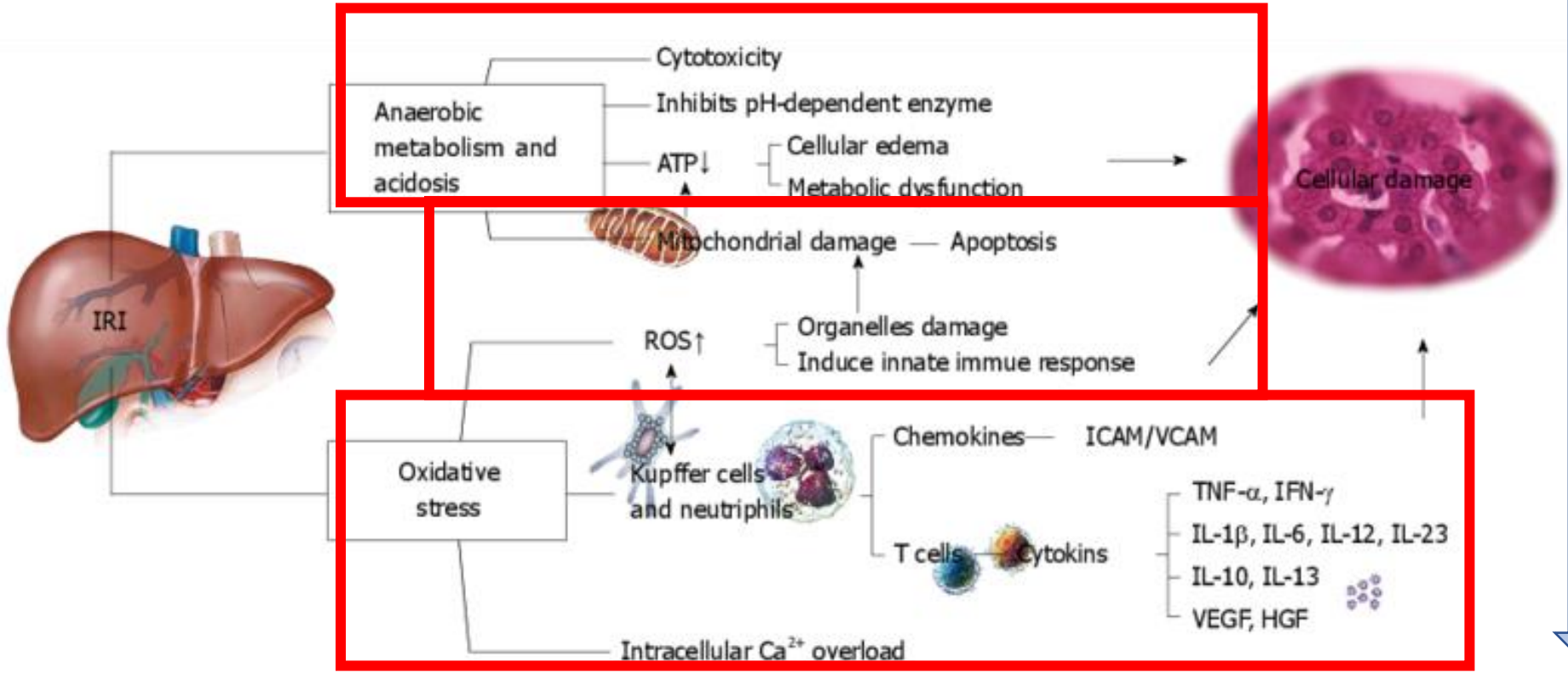
New frontiers on ex-vivo organ perfusion

Ex-vivo perfusion and inflammatory mediators: The Liver

Davide Ghinolfi
Azienda Ospedaliero Universitaria Pisana
Pisa, Tuscany

Mechanisms of hepatic ischemia reperfusion injury

Guan LY. World Journal of Gastrointestinal Surgery. 2014 6(7):122-8



Ischemic cells released **DAMPs**

DAMPs activated **Kupffer cell**

Kupffer generate **pro-inflammatory cytokines and chemokines**

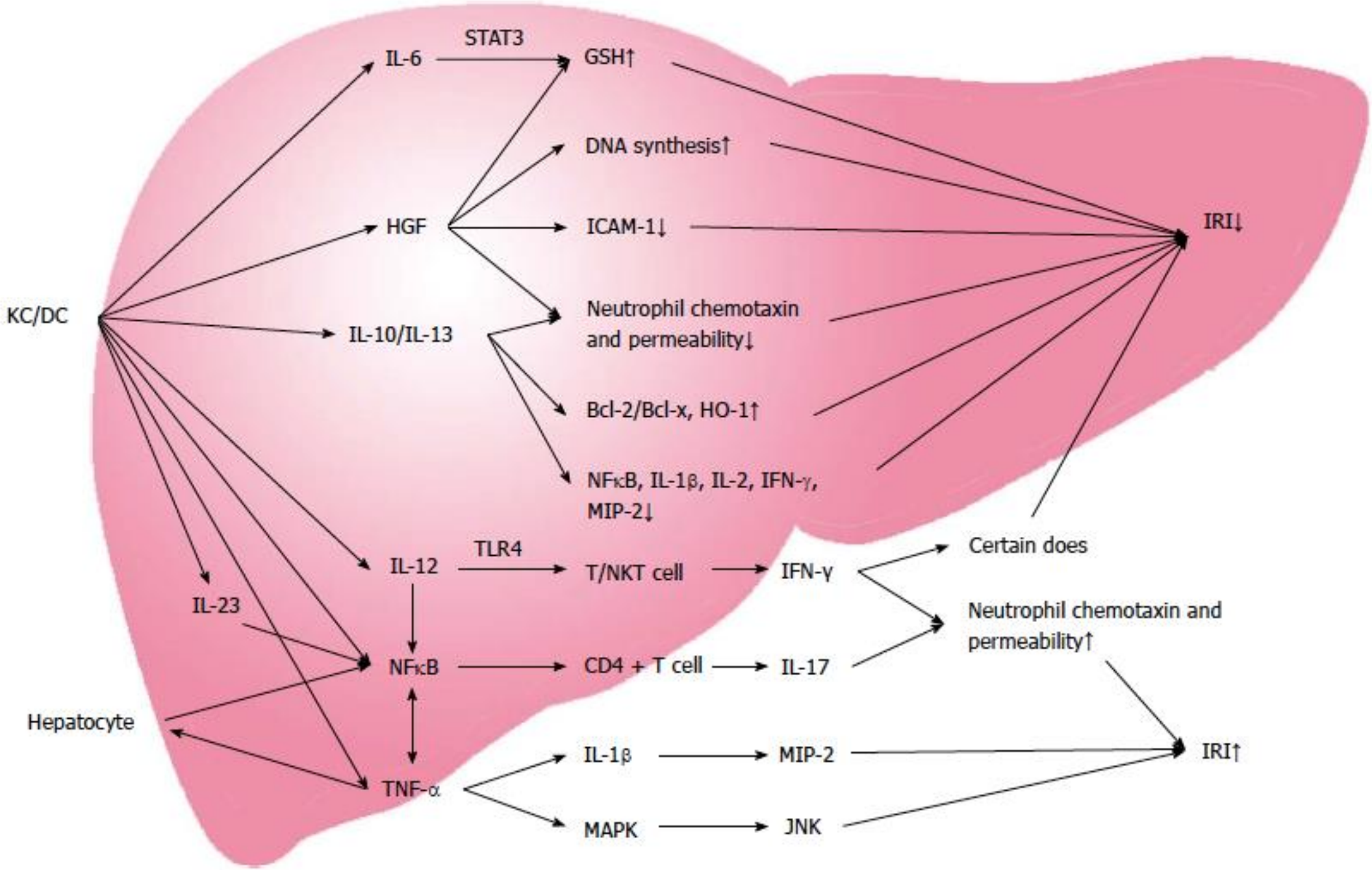
Chemokines guide intravascular neutrophil recruitment

Neutrophil generate firm adhesion

Loss of endothelial barrier **integrity**

Liver damage

- Ischemia leads to glycogen consumption, ATP depletion, cellular edema and metabolic dysfunction
- Mitochondrial ROS production, cell-death released DAMPs and activation of complements
- The reperfusion activates proinflammatory immune cascade



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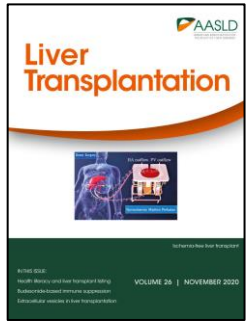
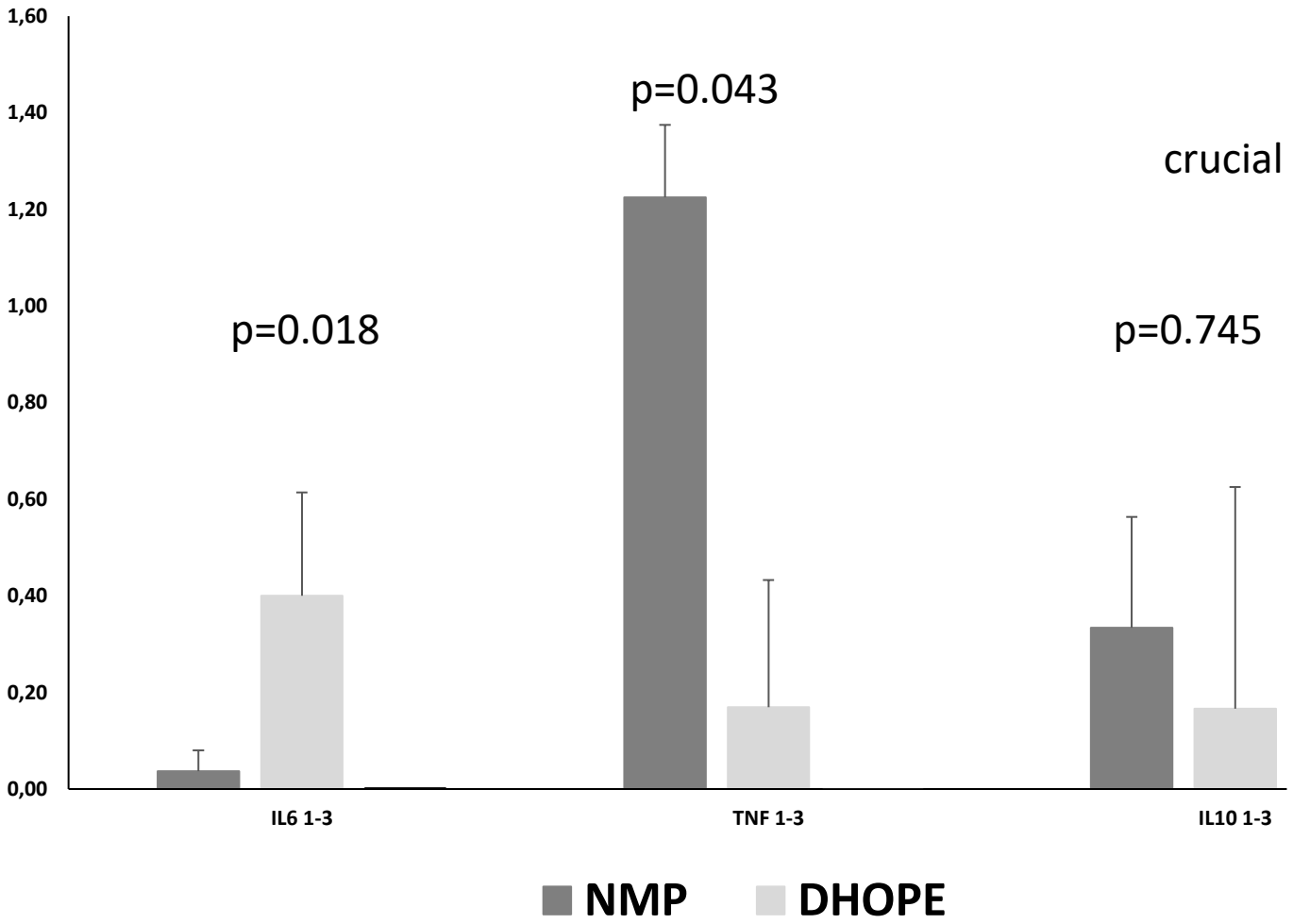


Sequential Use of Normothermic Regional and Ex Situ Machine Perfusion in Donation After Circulatory Death Liver Transplant

Davide Ghinolfi,[1*] Daniele Dondossola,[4,8*] Erion Rreka,[1] Caterina Lonati,[5] Daniele Pezzati,[1] Andrea Cacciatoinsilla,[9] Alessia Kersik,[4] Chiara Lazzeri,[10] Alberto Zanella,[6,8] Adriano Peris,[10] Marco Maggioni,[7] Giandomenico Biancofiore,[2] Paolo Reggiani,[4] Riccardo Morganti,[3] Paolo De Simone,[1] and Giorgio Rossi[4,8]



TNF-a in NMP

crucial factor in post-reperfusion syndrome

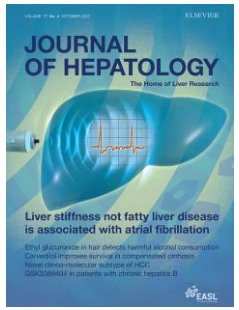
IL-6 in HOPE

higher risk of AKI

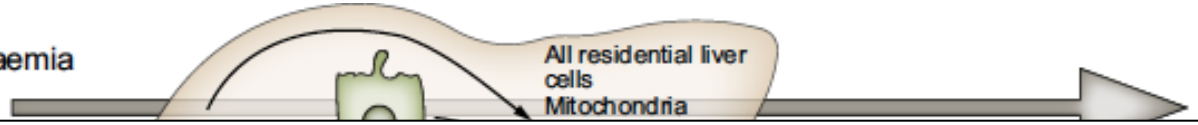
IL-6, TNF-α and IL-10 release ratio in perfusate during ex-situ machine perfusion

Protective mechanisms and current clinical evidence of hypothermic oxygenated machine perfusion (HOPE) in preventing post-transplant cholangiopathy

Andrea Schlegel[1,3], Robert J. Porte[2], Philipp Dutkowski[1,*]



Warm and cold ischaemia
= hypoxia



Reperfusion
= reintroduction of oxygen

Reperfusion-injury = temperature-dependent

Normothermic reperfusion after ischaemia (Hypoxia)

Hypothermic reperfusion after ischaemia (Hypoxia)

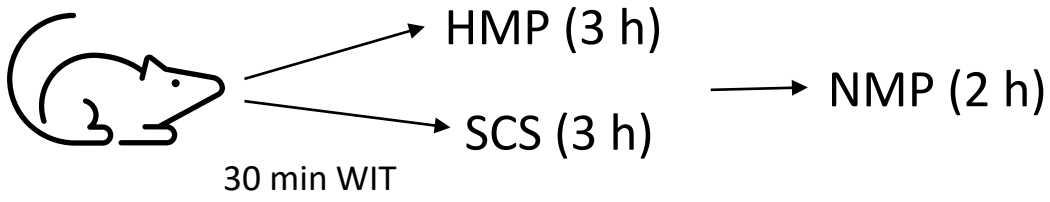
Full picture of reperfusion injury with complex I injury, subsequent ROS and FMN release, downstream inflammation and activation of the innate immune system

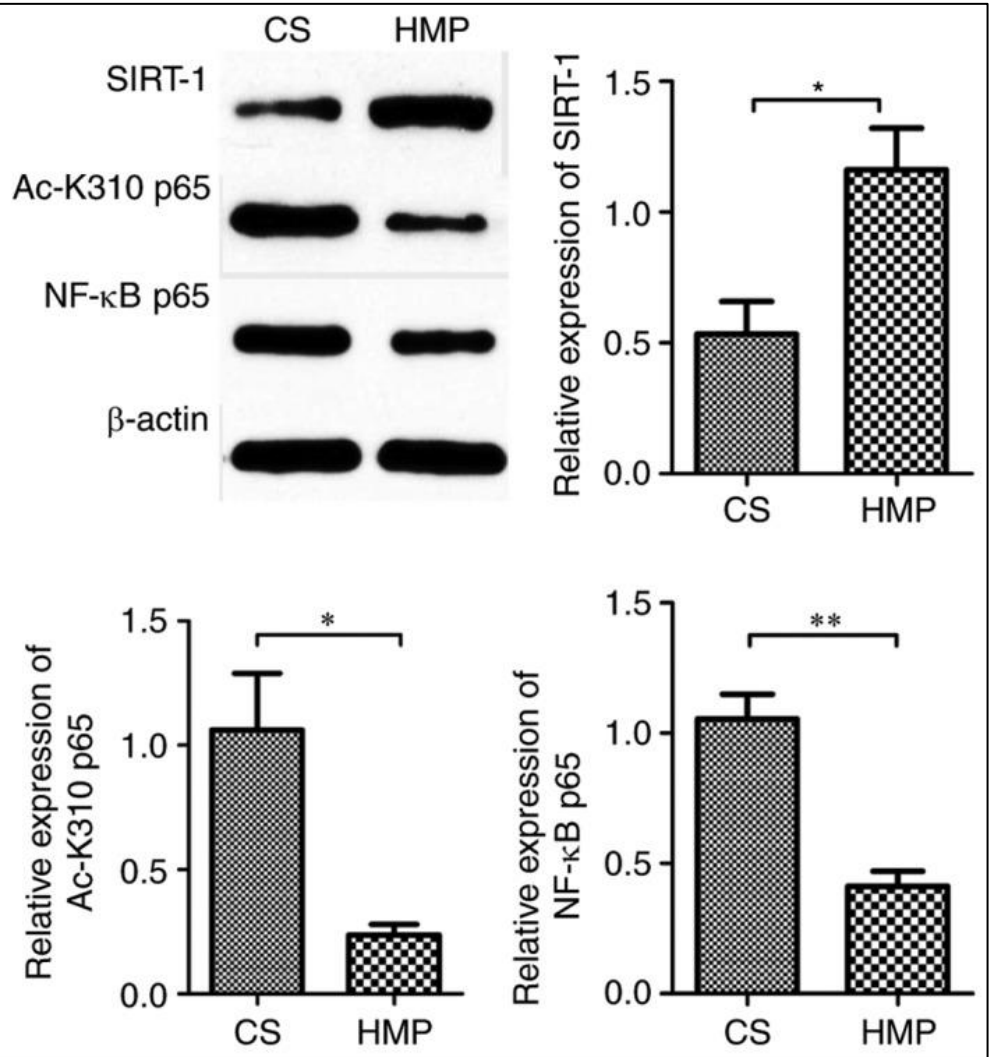
Reduced reperfusion injury due to: reconditioning of respiratory chain

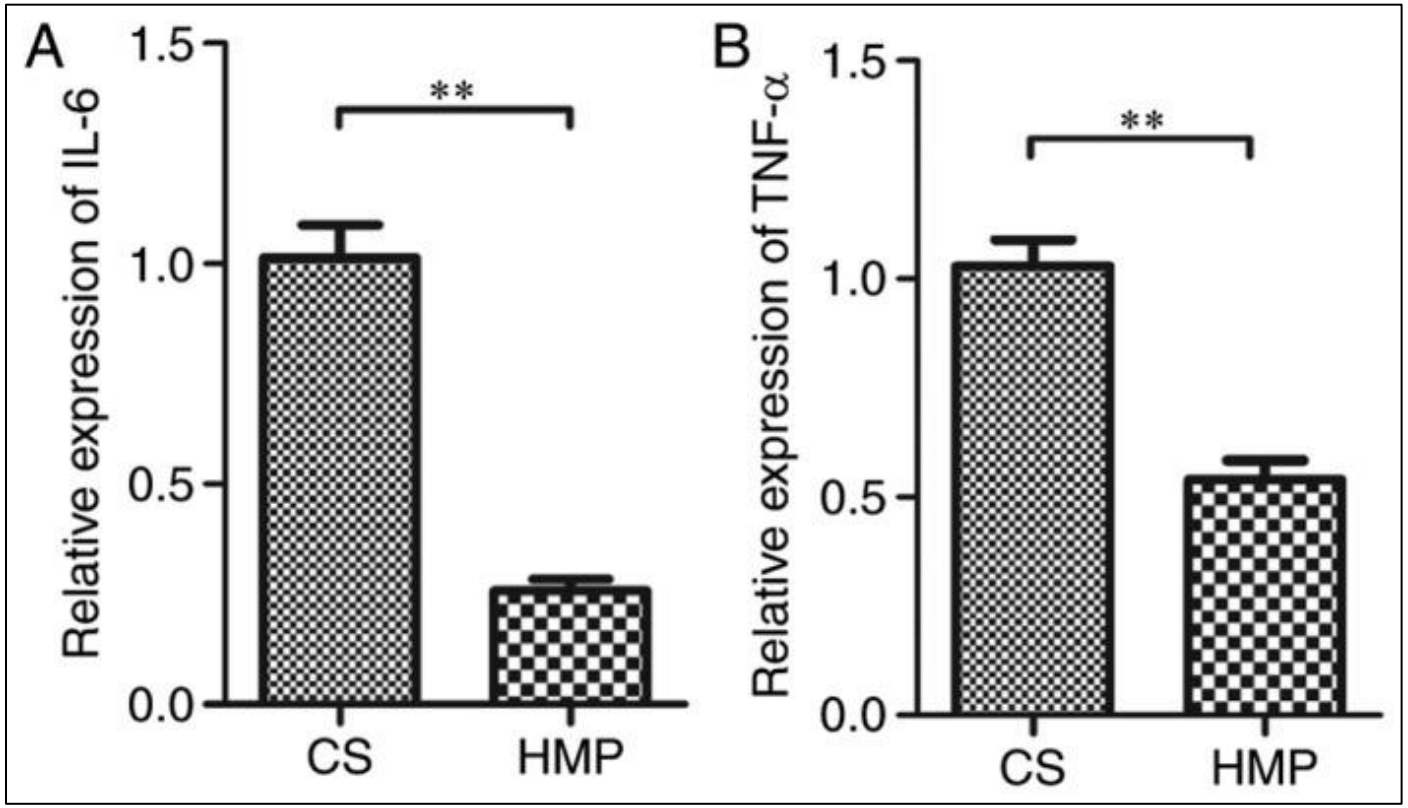
- Slow metabolism of succinate
- Low ROS and FMN release
- Re-establishment of electron flow
- ATP Recharging
- With low cellular metabolic need

Hypothermic machine perfusion ameliorates inflammation during ischemia-reperfusion injury via sirtuin-1-mediated deacetylation of nuclear factor-κB p65 in rat livers donated after circulatory death

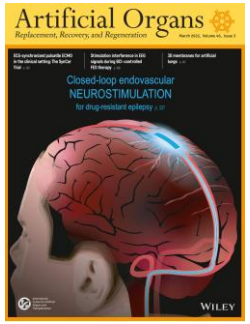
CHENG ZENG[1-4], XIAOYAN HU[1-4], WEIYANG HE[1-4], YANFENG WANG[1-4], LING LI[1-4], YAN XIONG[1-4] and QIFA YE[1-5]







The mRNA expression of NF-κB p65, IL-6 and TNF-α was significantly decreased in the HMP group compared with CS samples.
These results indicate that HMP may reduce the inflammatory response during IRI via SIRT-1-mediated deacetylation of NF-κB p65.

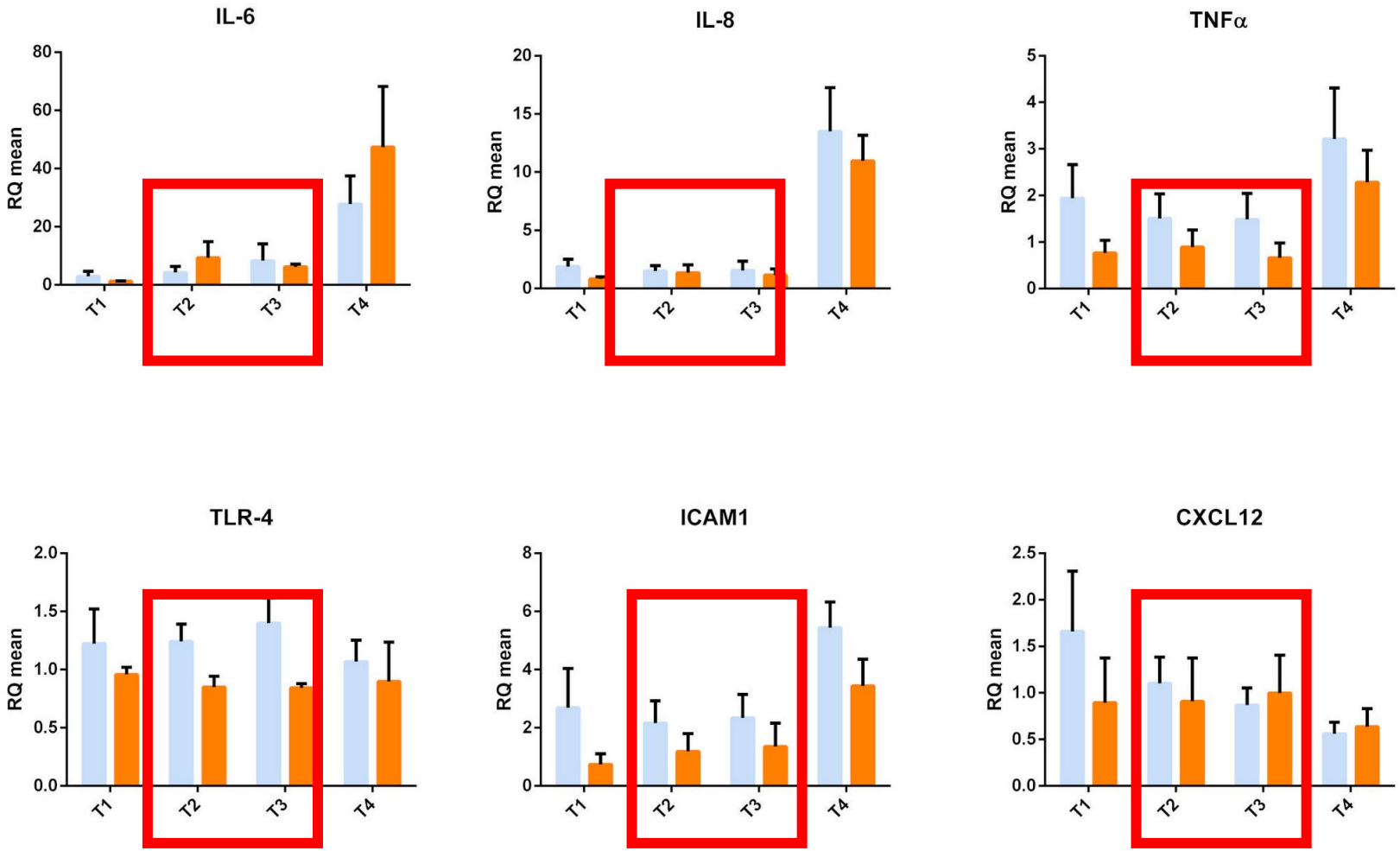


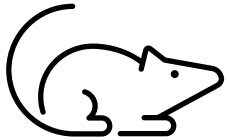
Clinical assessment of liver metabolism during hypothermic oxygenated machine perfusion using microdialysis

10 grafts D-HOPE
MD and perfusate evaluation (glucose, lactate, piruvate, glutamate) correlated to clinical outcome

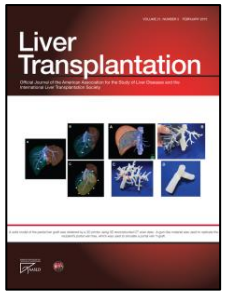
No correlation between
MD and perfusate parameters and the expression of inflammatory cytokines or adhesion molecules (IL-6, IL-8, TNF, TLR-4, ICAM-1, CXCL12)

No correlation between inflammatory cytokines during DHOPE and clinical outcome(EAD)





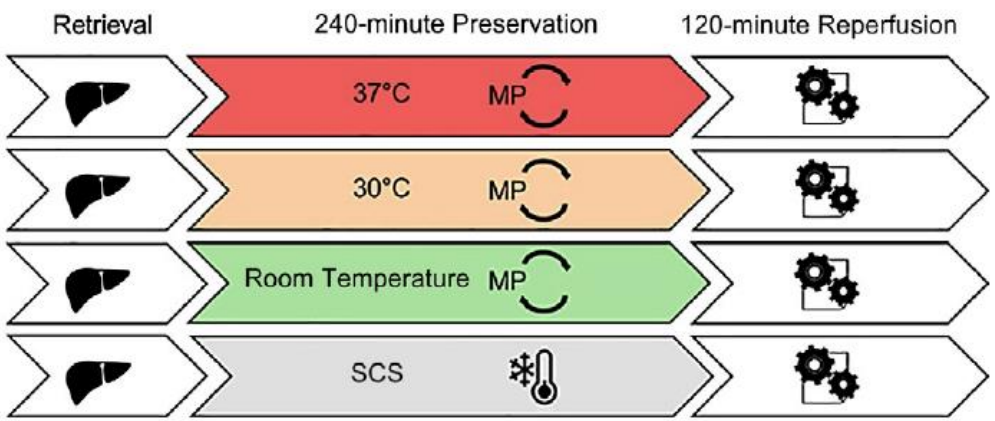
N=6

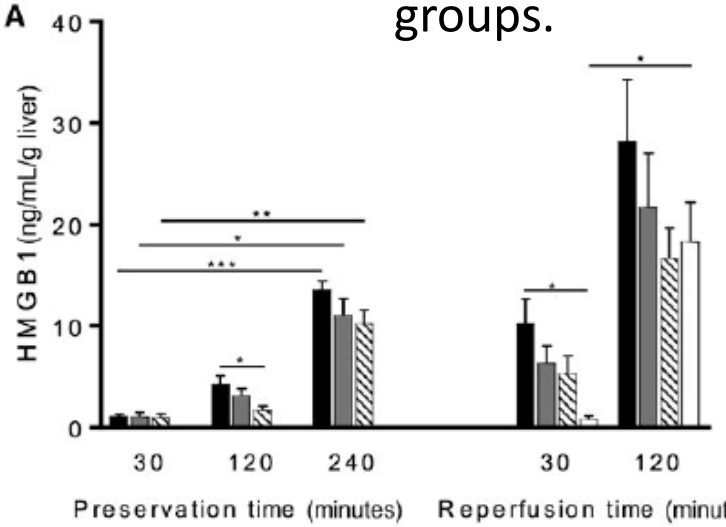


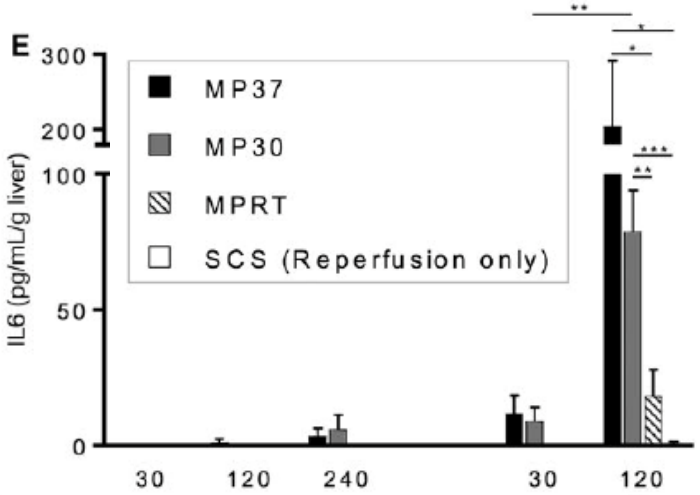
Damage-Associated Molecular Patterns Induce Inflammatory Injury During Machine Preservation of the Liver: Potential Targets to Enhance a Promising Technology

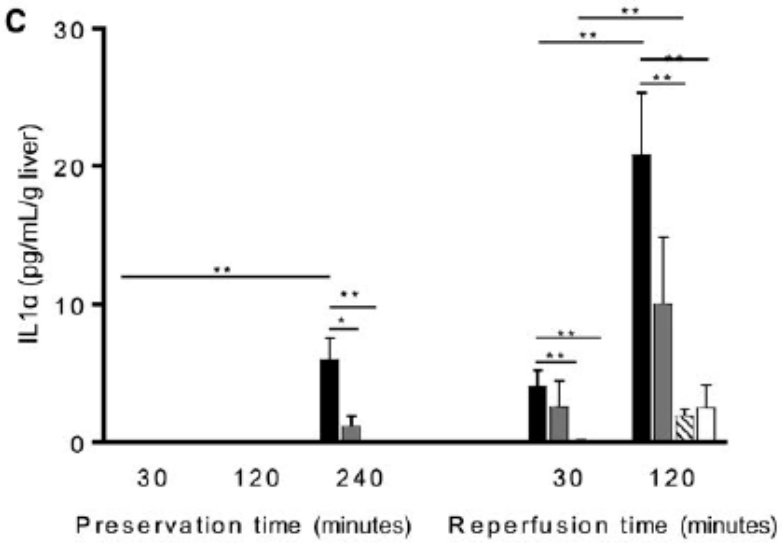
During MP37 a time-dependent increase of inflammatory biomarkers was observed.

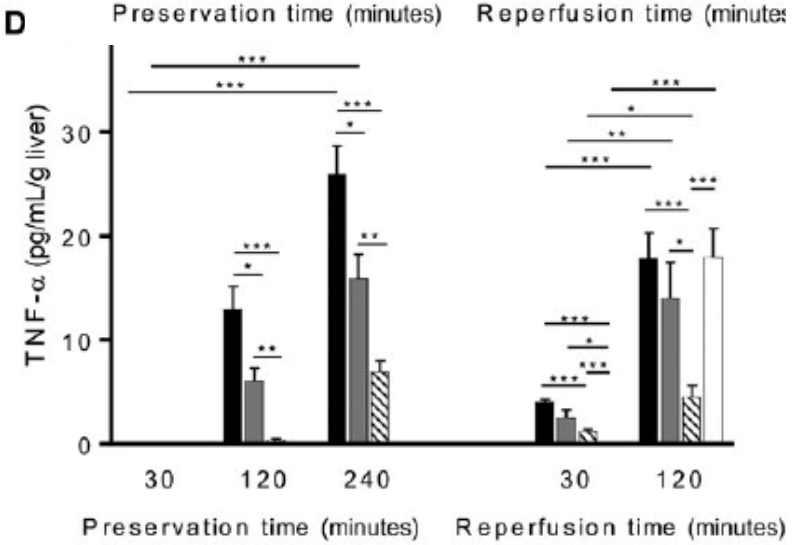
Cytokine levels correlated with graft metabolic rate with highest mean levels in the MP37 group and a stepwise reduction in levels for the MP30 and MPRT groups.

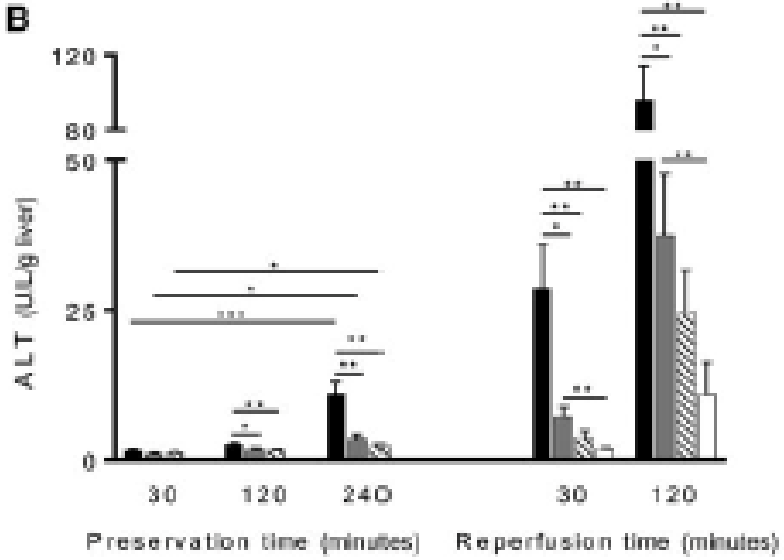












The Effect of Normothermic Machine Perfusion on the Immune Profile of Donor Liver

6 human livers in NMP for 6 hours

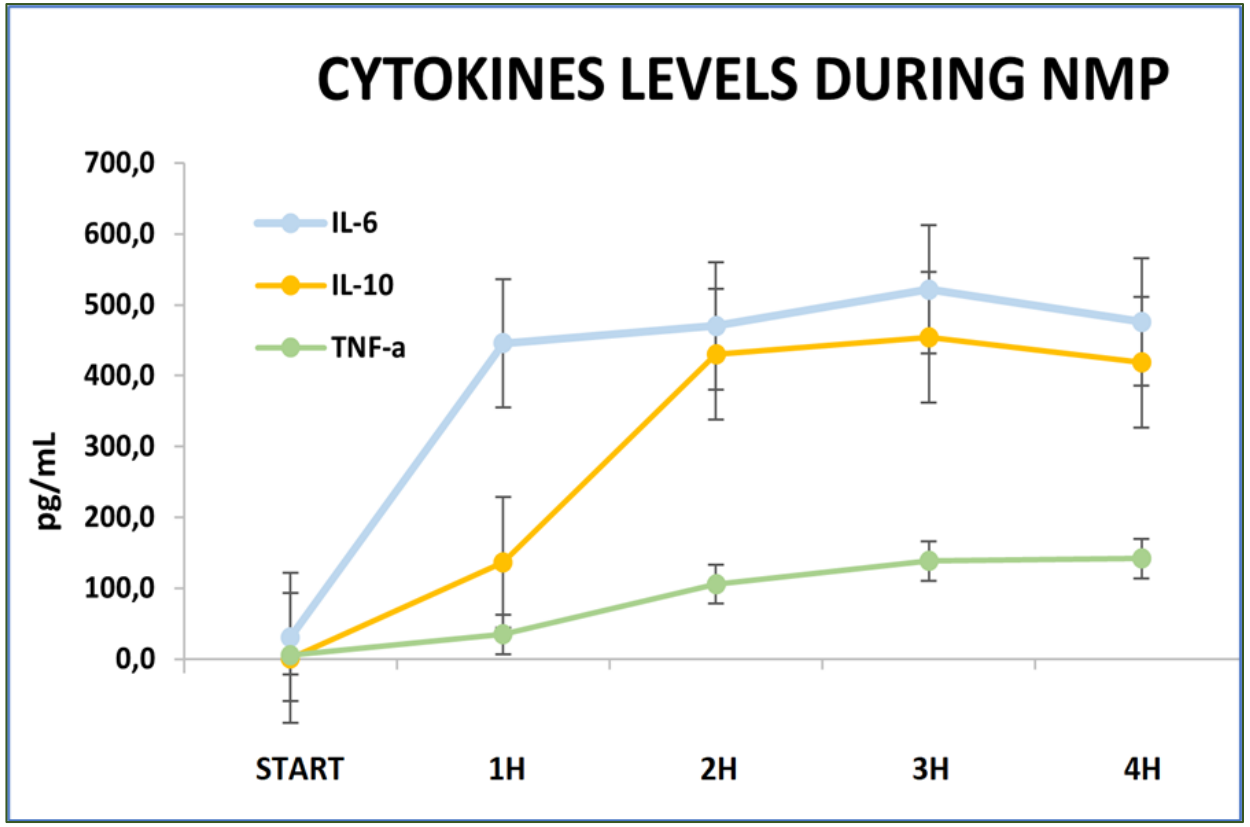
TABLE 2 | Cytokine concentrations (pg/mL) in human livers during 6 hour of normothermic machine perfusion.

	Hour 0 of NMPConcentration (pg/mL)	Hour 1 of NMPConcentration (pg/mL)	1H vs 0H P-value	Hour 3 of NMPConcentration (pg/mL)	3H vs 0H P-value	3H vs 1H P-value	Hour 6 of EVLPConcentration (pg/mL)	6H vs 0H P-value	6H vs 1H P-value
IL-1b	8.39 ± 11.08	1.92 ± 0.77	0.226	37.14 ± 26.06	0.086	0.029	252.16 ± 261.41	0.095	0.085
IL-2	1.47 ± 0.43	3.04 ± 1.28	0.023	13.54 ± 7.44	0.016	0.020	37.45 ± 45.91	0.140	0.150
IL-4	0.60 ± 0.80	5.21 ± 3.44	0.037	25.44 ± 3.13	0.000	0.000	24.27 ± 2.91	0.000	0.000
IL-6	14.10 ± 8.12	567.37 ± 628.36	0.106	26368.84 ± 17769.95	0.021	0.020	24707.60 ± 17412.95	0.025	0.025
IL-8 (CXCL8)	43.40 ± 73.04	2815.07 ± 3103.37	0.105	2835.61 ± 1563.92	0.012	0.989	785.97 ± 267.48	0.002	0.197
IL-10	0.19 ± 0.12	186.28 ± 128.71	0.023	3223.56 ± 2154.59	0.020	0.025	4686.07 ± 2901.50	0.015	0.016
IL-17A (CTLA-8)	0.09 ± 0.13	0.22 ± 0.03	0.194	4.00 ± 5.32	0.163	0.180	19.22 ± 21.92	0.108	0.110
G-CSF (CSF-3)	1.58 ± 2.38	0.94 ± 1.80	0.614	1088.88 ± 318.49	0.001	0.001	2482.11 ± 688.53	0.000	0.000
IFN-gamma	0.20 ± 0.12	0.21 ± 0.16	0.941	6.90 ± 5.30	0.038	0.035	220.75 ± 245.05	0.100	0.100
GM-CSF	2.04 ± 0.95	5.91 ± 2.99	0.025	27.11 ± 5.76	0.000	0.000	53.31 ± 35.74	0.023	0.030
TNF-alpha	0.03 ± 0.07	205.68 ± 233.06	0.104	2633.87 ± 2027.38	0.034	0.031	1488.60 ± 1331.19	0.054	0.056
MCP-1 (CCL2)	220.74 ± 117.06	916.22 ± 736.96	0.109	3200.63 ± 3030.23	0.075	0.169	1622.62 ± 706.26	0.006	0.136
MIP-2a (CXCL2)	4.56 ± 4.83	526.88 ± 589.60	0.105	2040.39 ± 1209.96	0.013	0.022	1930.59 ± 996.82	0.008	0.017
GROa (CXCL1)	1.28 ± 2.70	76.63 ± 65.93	0.054	377.16 ± 106.55	0.001	0.001	297.82 ± 69.17	0.000	0.000
Granzyme A	29.80 ± 30.54	61.97 ± 55.69	0.291	87.56 ± 54.01	0.012	0.310	114.26 ± 66.80	0.022	0.019
Granzyme B	5.04 ± 1.19	9.97 ± 4.53	0.078	9.54 ± 4.24	0.071	0.880	125.79 ± 139.88	0.112	0.127

Significantly increased of pro-inflammatory and anti-inflammatory cytokines during NMP

Perfusate cytokines profiles during liver grafts ex-situ normothermic perfusion

26 grafts (16 DBD, 10 DCD)
4 h NMP
IL-6, IL-10, TNF-α perfusate analysis



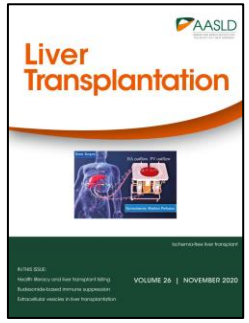
Cytokines profiles stabilize 3-hours after commencing NMP

- **IL-6 RR in older donors**
- **IL-10 RR in DCD Donors**
- **TNF-α in donors with higher vasopressors requirements**

IL-10 RR is associated to acute kidney injury (AKI) after LT

In viable liver grafts, IL-6, IL-10 and TNF-a release ratio and absolute concentrations do not correlate to PRS, graft or patient survival

Cytokines concentration: the effect or the consequence ?
Controlling cytokine production could be used to improve the performance of NMP (???)



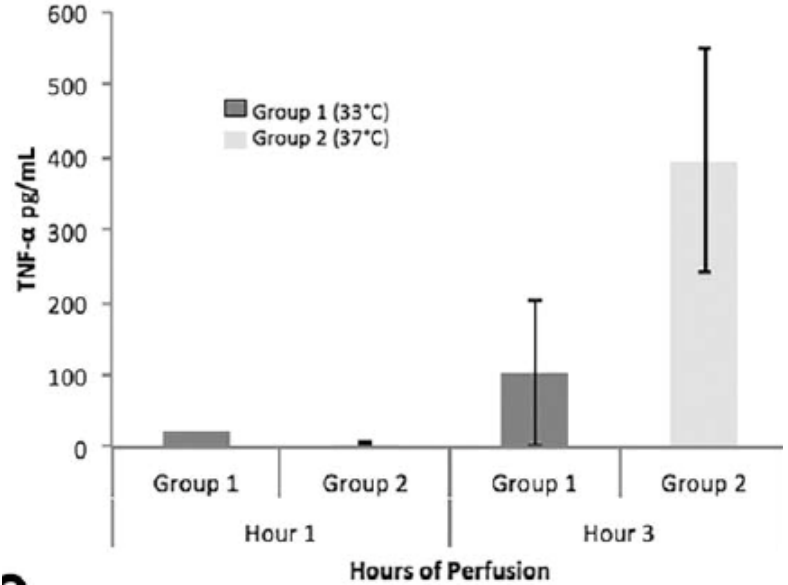
Anti-inflammatory Signaling During Ex Vivo Liver Perfusion Improves the Preservation of Pig Liver Grafts Before Transplantation

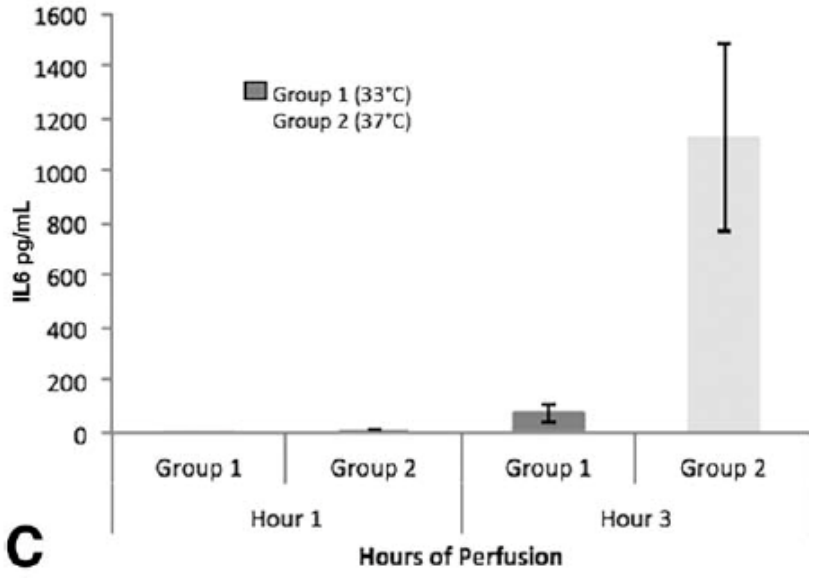
Nicolas Goldaracena,[1] Juan Echeverri,[1,4] Vinzent N. Spetzler,[1] Johan M. Kaths,[1] Andrew S. Barbas,[1] Kristine S. Louis,[1] Oyedele A. Adeyi,[2] David R. Grant,[1] Nazia Selzner,[3] and Markus Selzner[1]

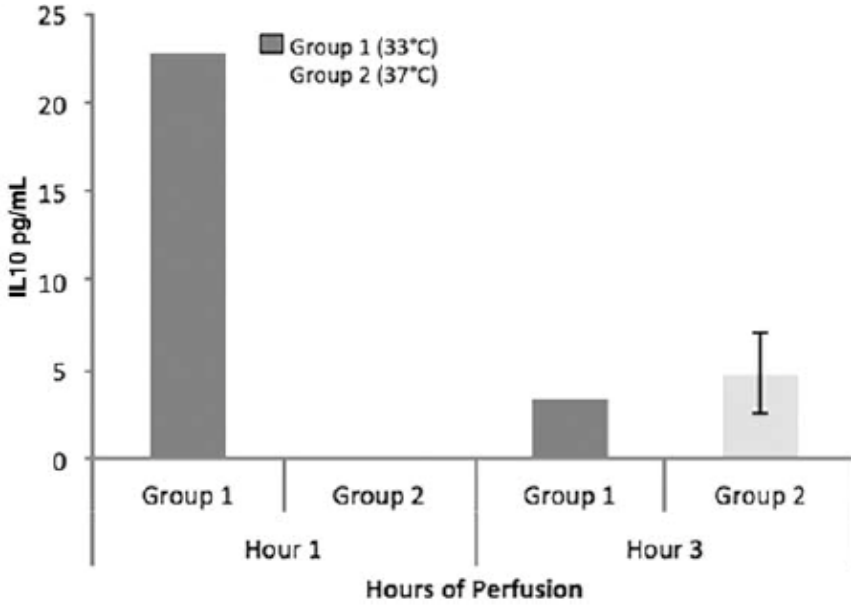
2h SCS	4h SNMP+drugs	LT
2h SCS	2h NMP	LT
6h SCS		LT

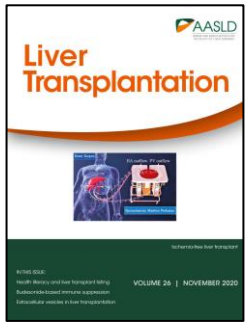
Group 1:	Subnormothermic conditions (33°C) / PGE1 / Acetylcisteine / CO
Group 2:	Normothermic conditions (37°C)
Group 3:	Static cold storage (SCS) for 6 hours

Preservation









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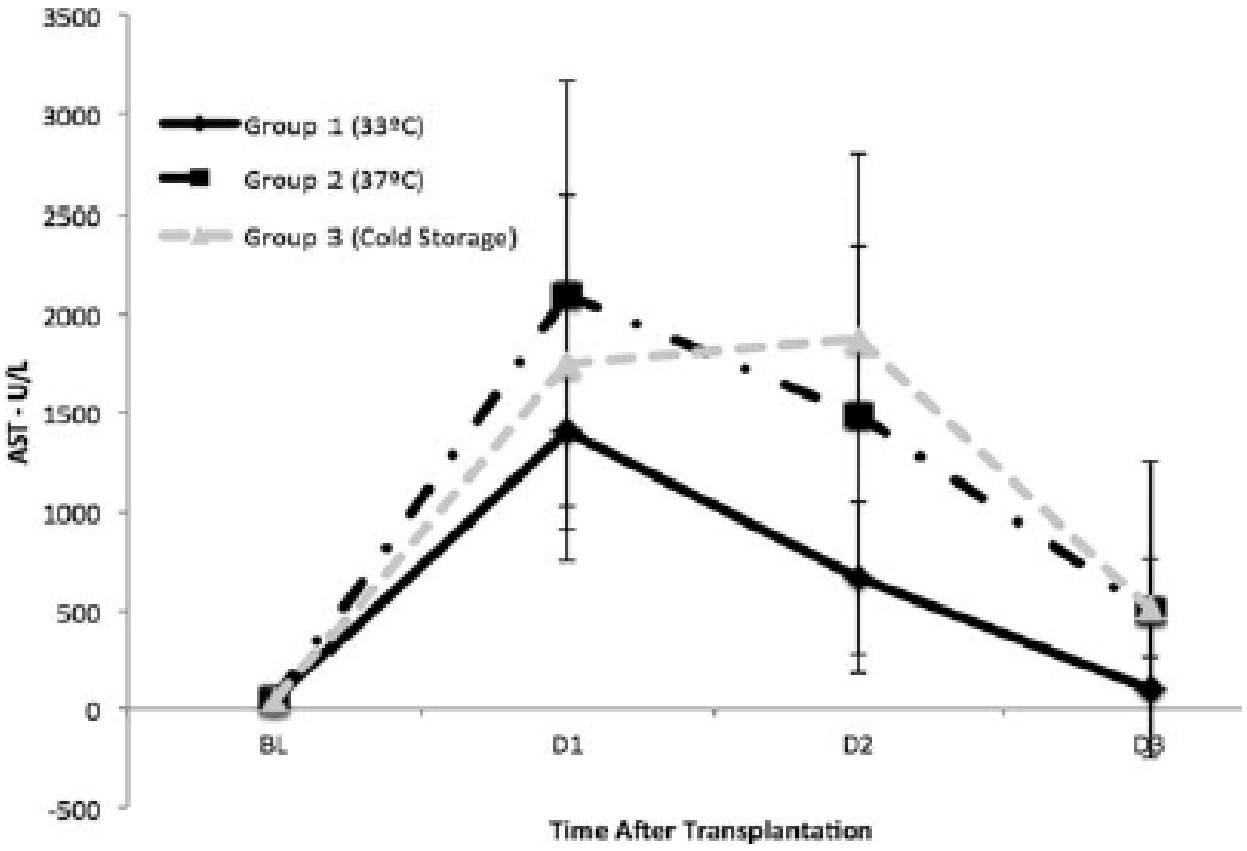
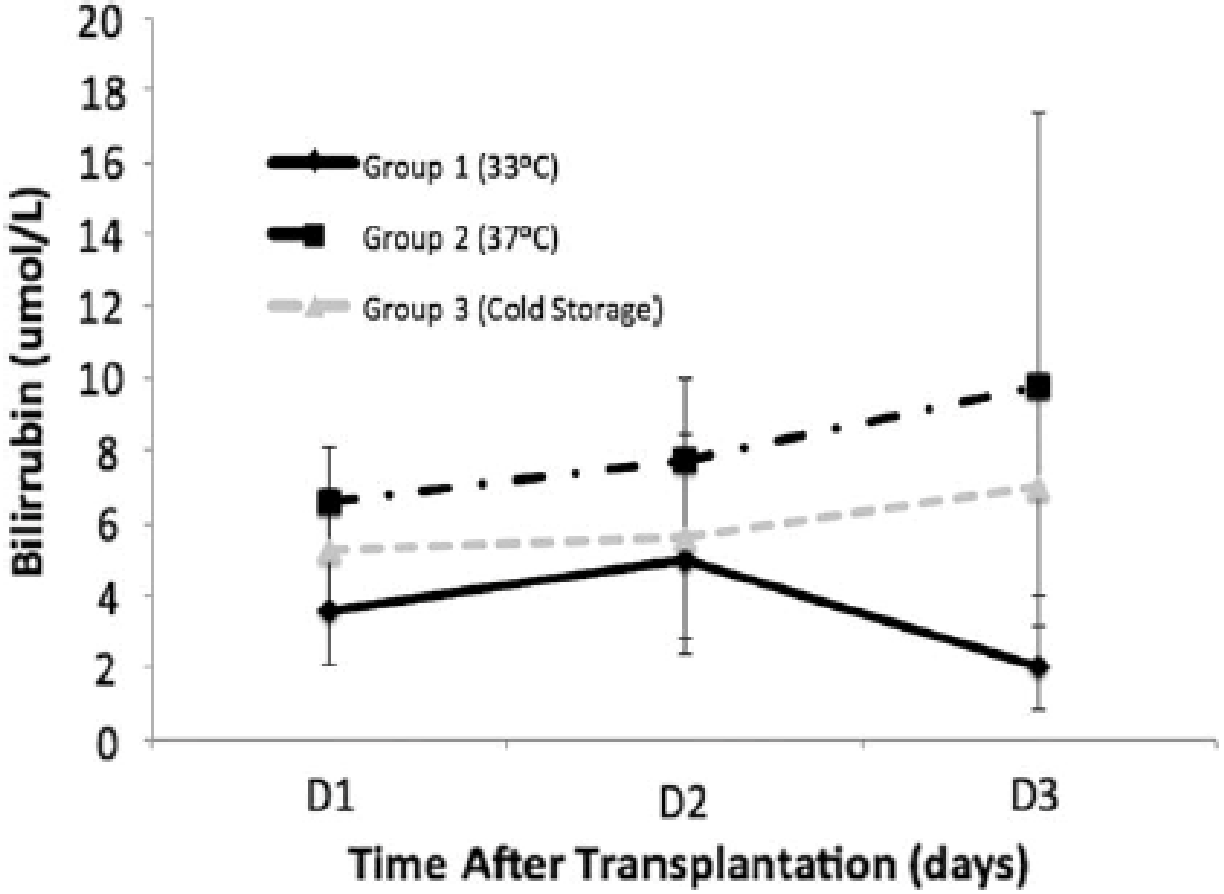
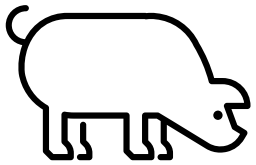
Transplant



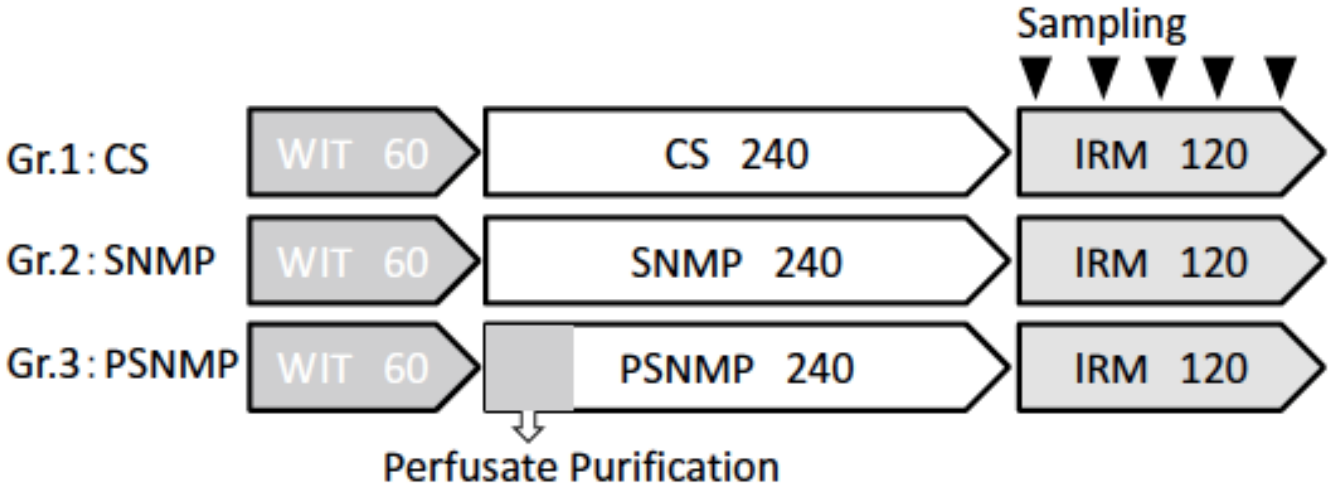


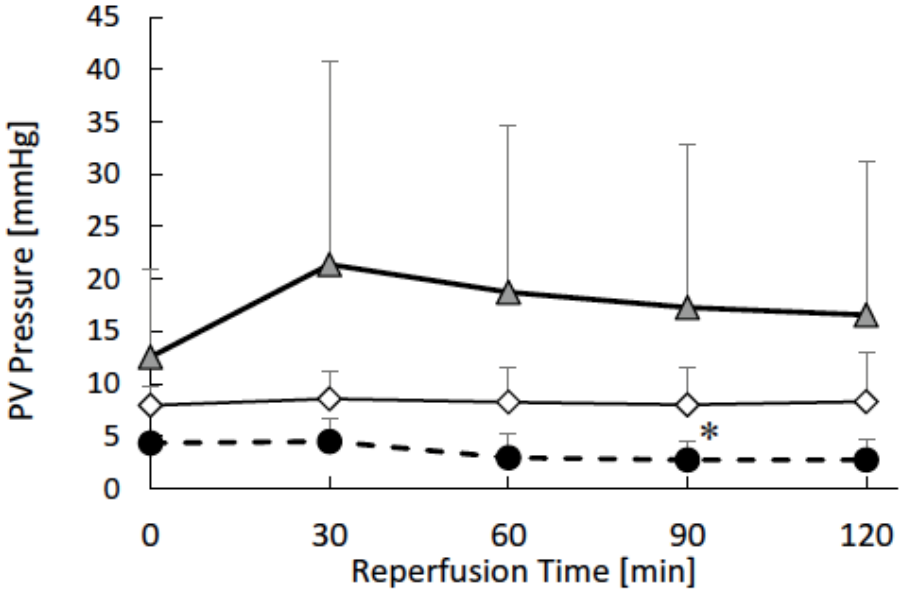
Initial perfusate purification during subnormothermic machine perfusion for porcine liver donated after cardiac death

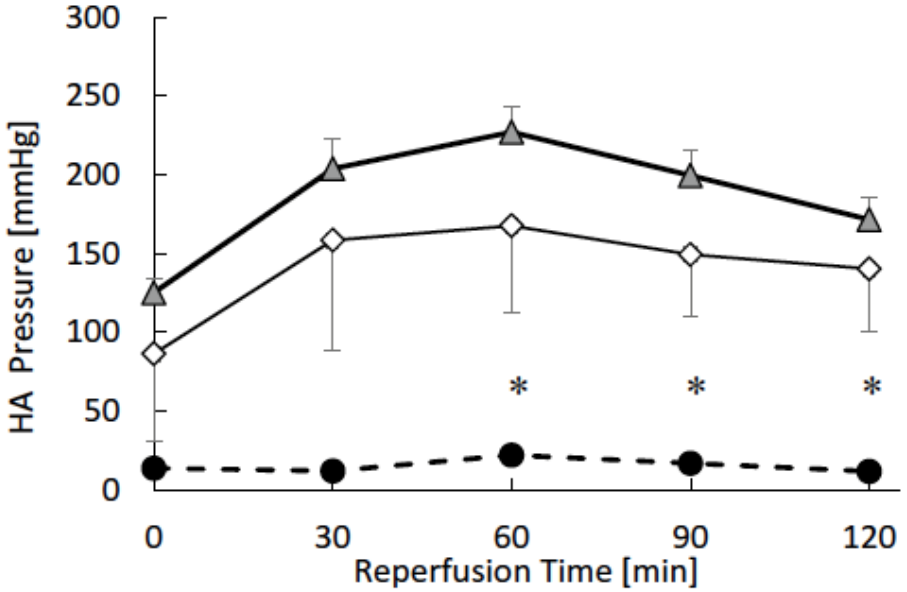
Hiromichi Obara[1,2,3] · Noriyuki Morito[1] · Naoto Matsuno[1,2,3] · Ryo Yoshikawa[1] · Tetsuya Nakajo[4] · Mikako Gochi[2]
Masahide Otani[2] · Tatsuya Shonaka[2] · Hiroyuki Furukawa[2] · Toshihiko Hirano[5] · Shin Enosawa[3]

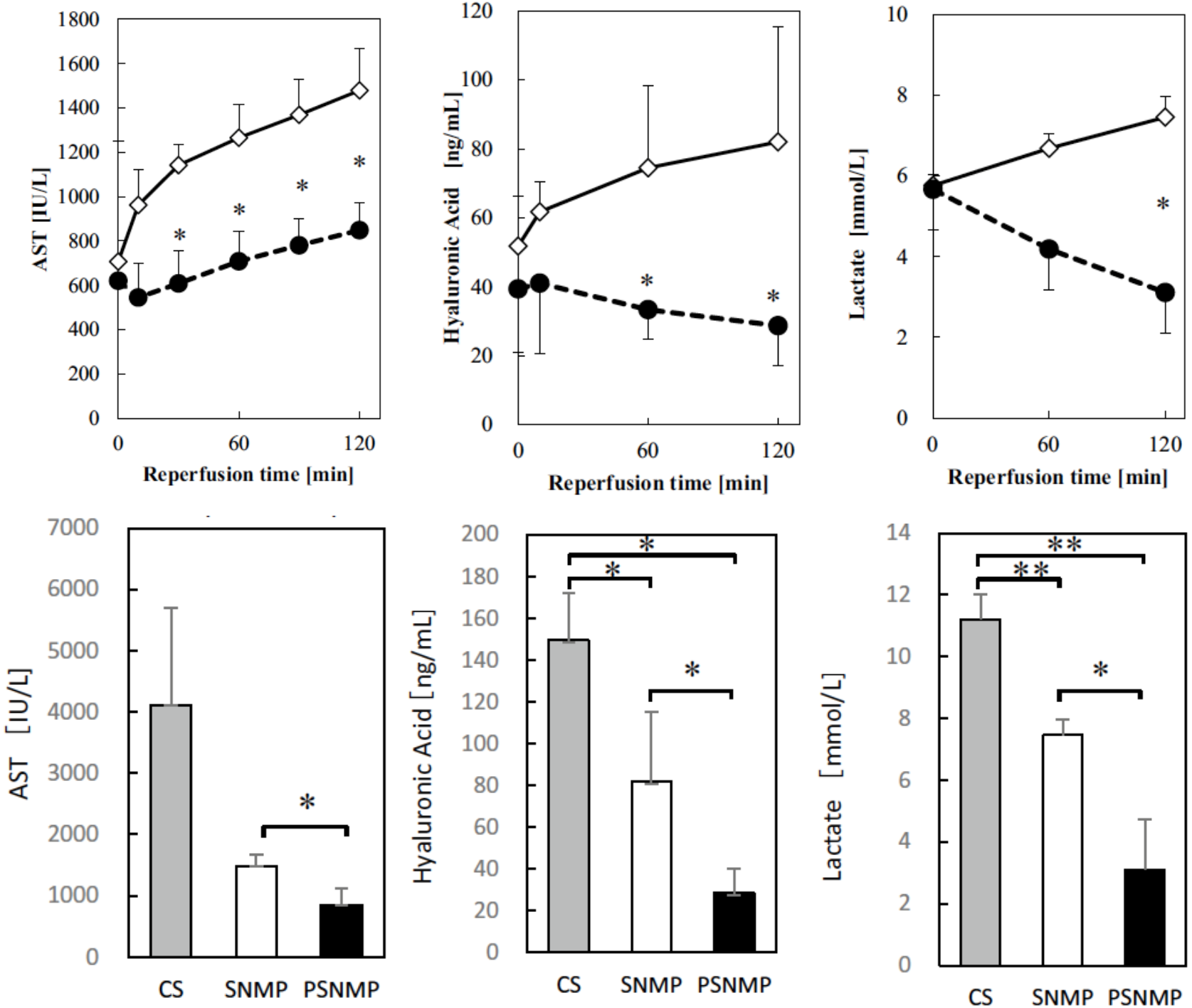


Flow rates maintained:
PV 0.22 mL/min/gr
HA 0.06 mL/min/gr









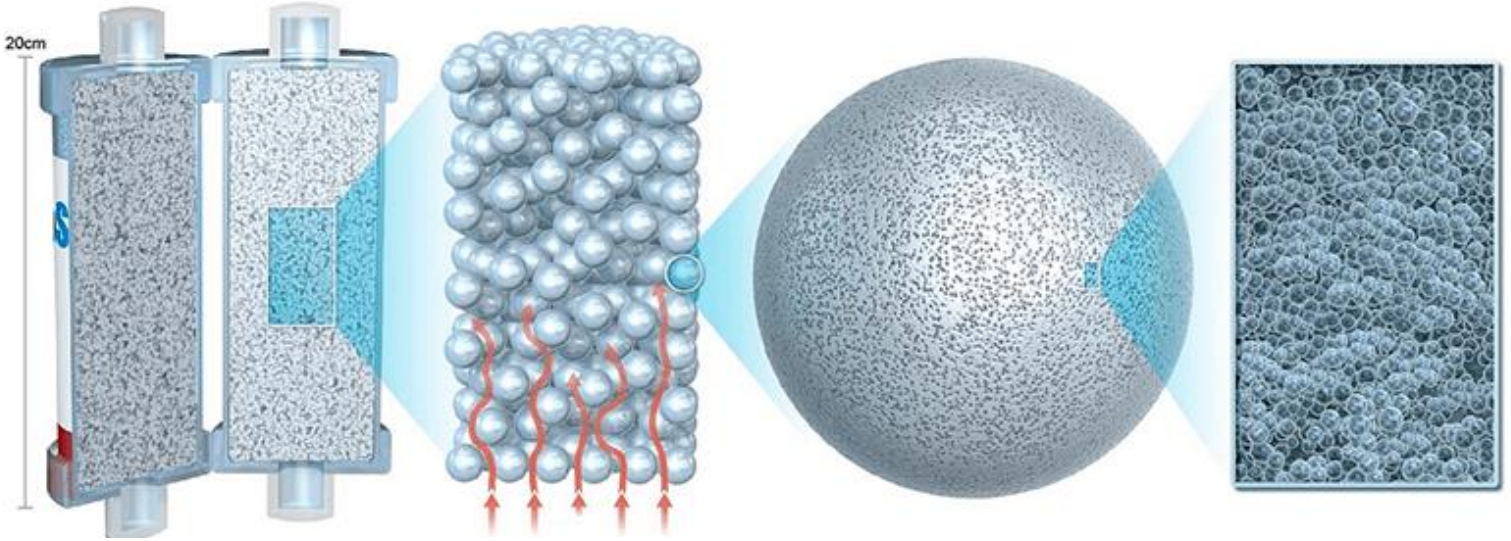
CS

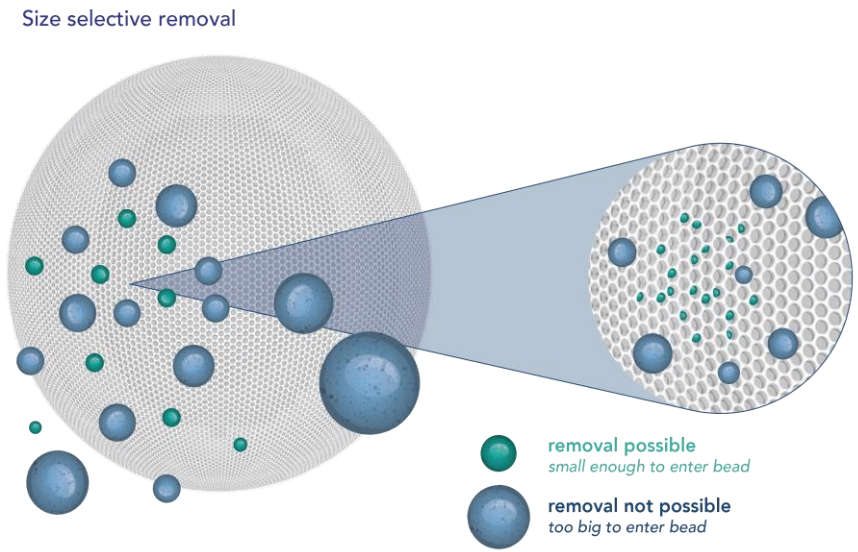
SNMP

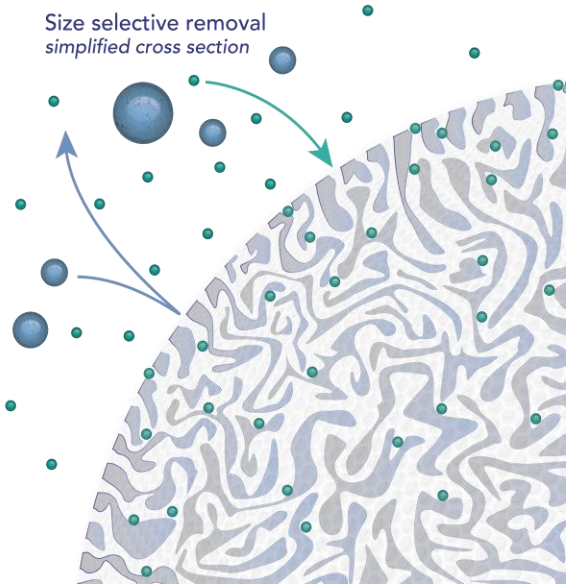
PSNMP

* p<0.05, ** p<0.01

Perfusion liquid purification: removal of cytokines as a new opportunity?







- Porous Polymer-based structure for hydrophobic molecules adsorption
- Wide adsorption spectrum: hydrophobic molecules up to 55kDa are adsorbed

Perfusate inflammatory mediators removal might be a strategy to minimize organ injury

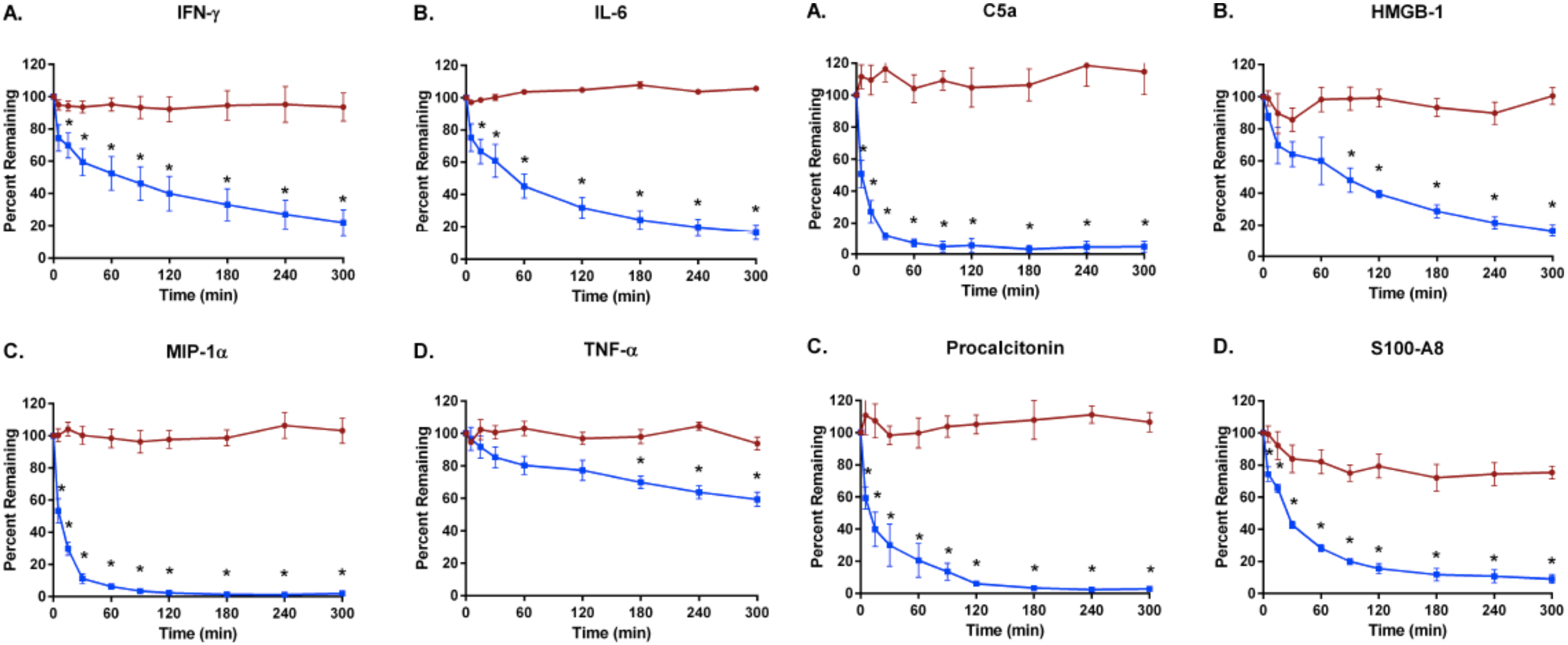
Kogelmann K, Jarczak D, Scheller M, Drüner M. Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care. 2017;21((1)):74

Inflammatory mediators adsorption in vitro: mechanisms

Cytokines Adsorption

Control CS

DAMPs Adsorption

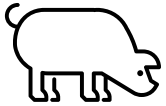


CS can efficiently remove of a broad spectrum of toxic cytokines and DAMPS from blood

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.

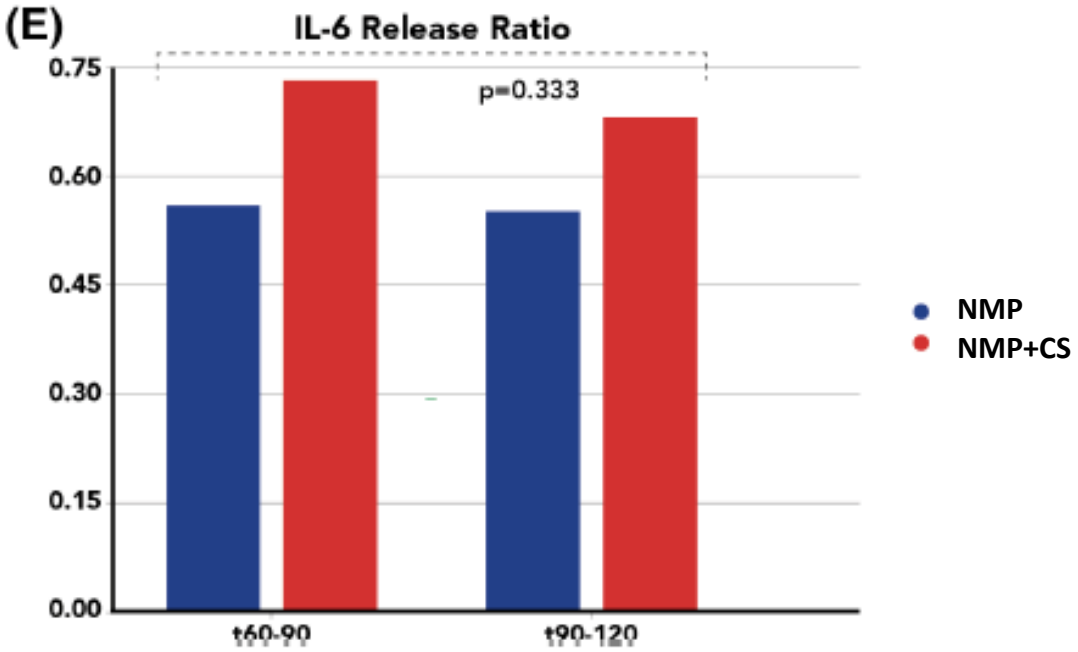
A new ex-situ machine perfusion device. A preliminary evaluation using a model of donors after circulatory death pig livers

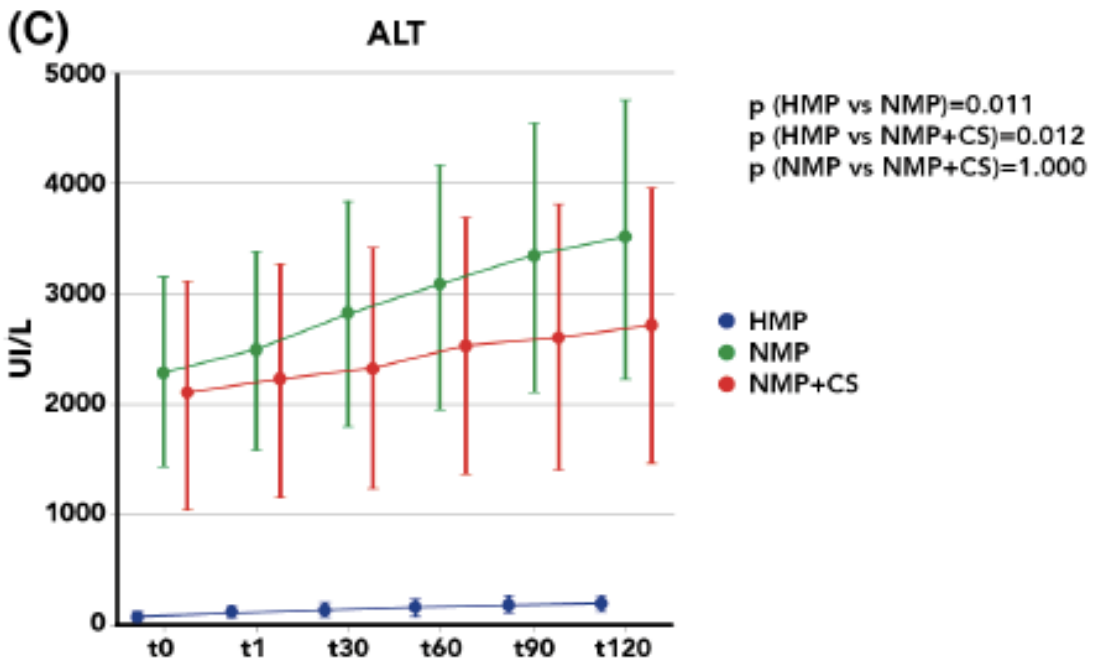
Davide Ghinolfi[1] | Fabio Melandro[1] | Damiano Patrono[2] | Quirino Lai[3] | Riccardo De Carlis[4] | Stefania Camagni[5] | Alessandro Gambella[6] | Franco Ruberto[3] | Paolo De Simone[1]

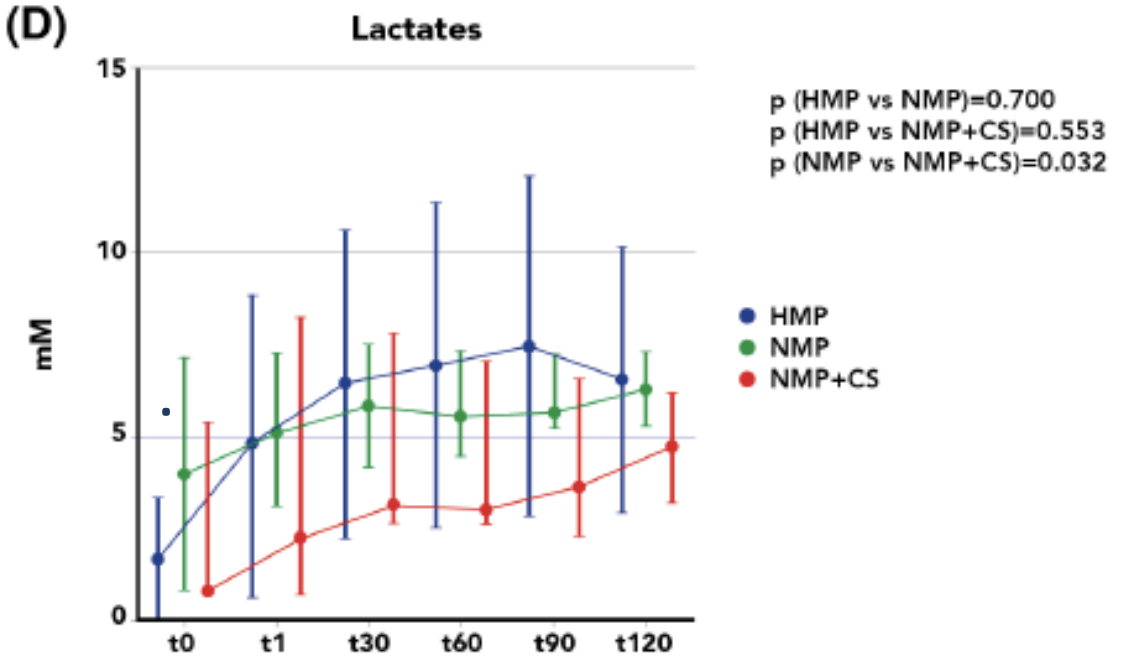


6 HMP
5 NMP
3 NMP+CS

2 h MP







$$IL6\ mass\ balance = (\overline{C_{pre}} - \overline{C_{post}}) * flow * time = 493.106\ pg$$

- **Cytokine adsorption during liver MP is feasable and effective**
- **NMP+CS showed lower ALT and improved lactate clearance than NMP**

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

Pilot clinical trial

INCLUSION CRITERIA

Recipient

- ->18 aa
- -MELD <24

Donor

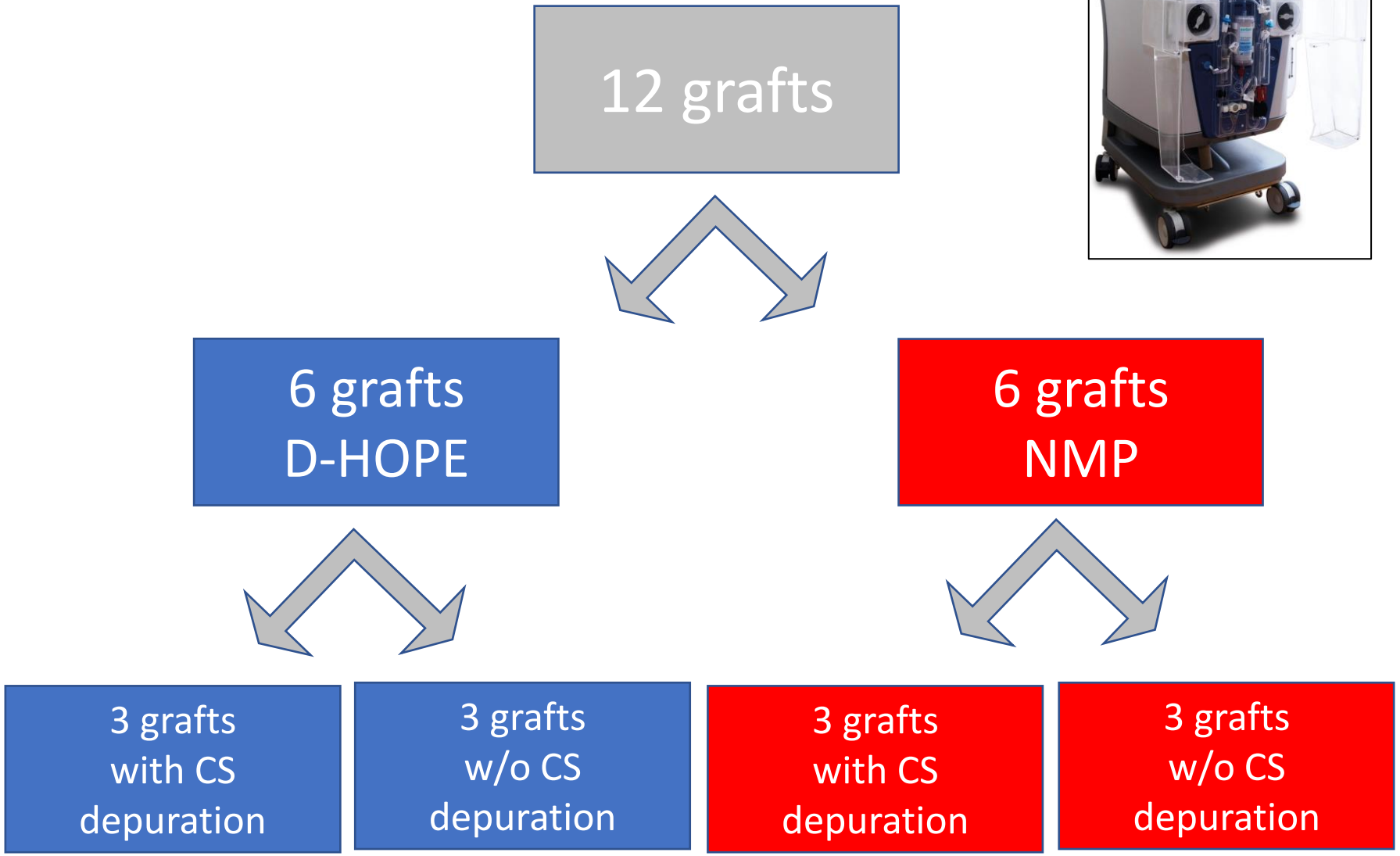
- ->80 yo
- -DBD
- -Viable for transplant

Primary target:

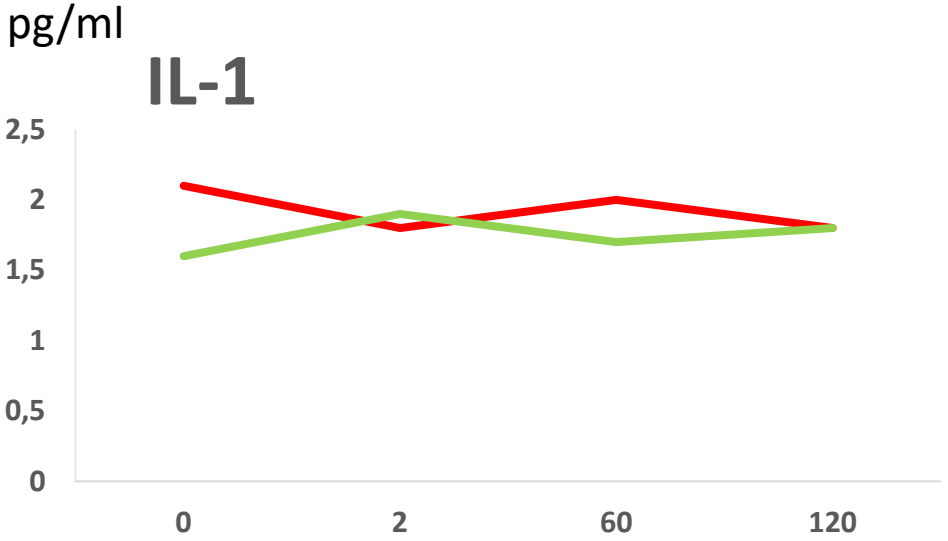
- -safety and feasibility

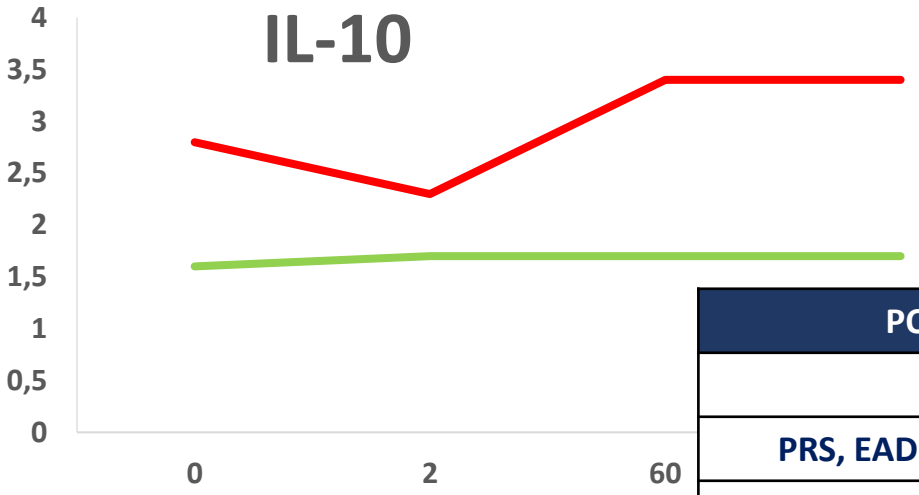
Secondary target

- -efficacy of CS
- -EM evaluation
- -clinical outcome



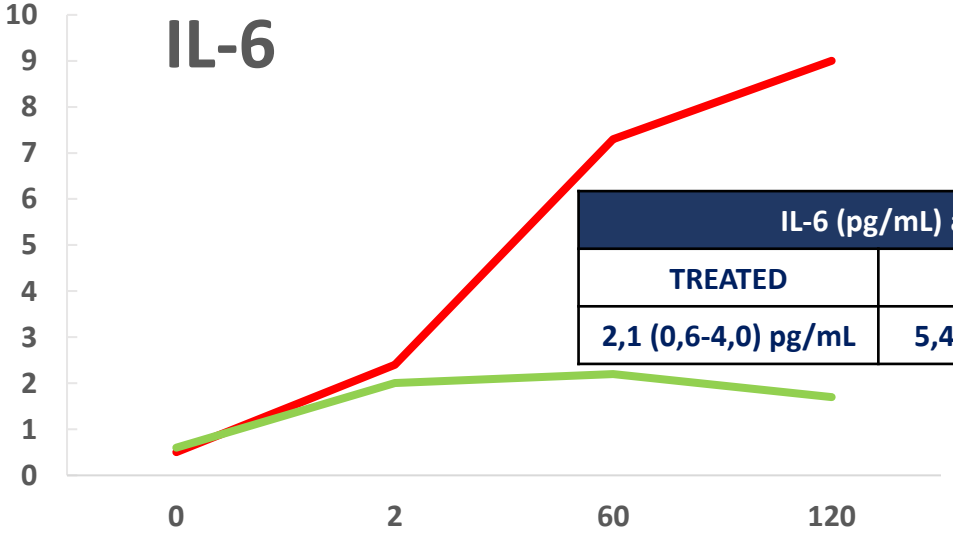
Perfusion liquid purification by cytokine adsorption in liver D-HOPE



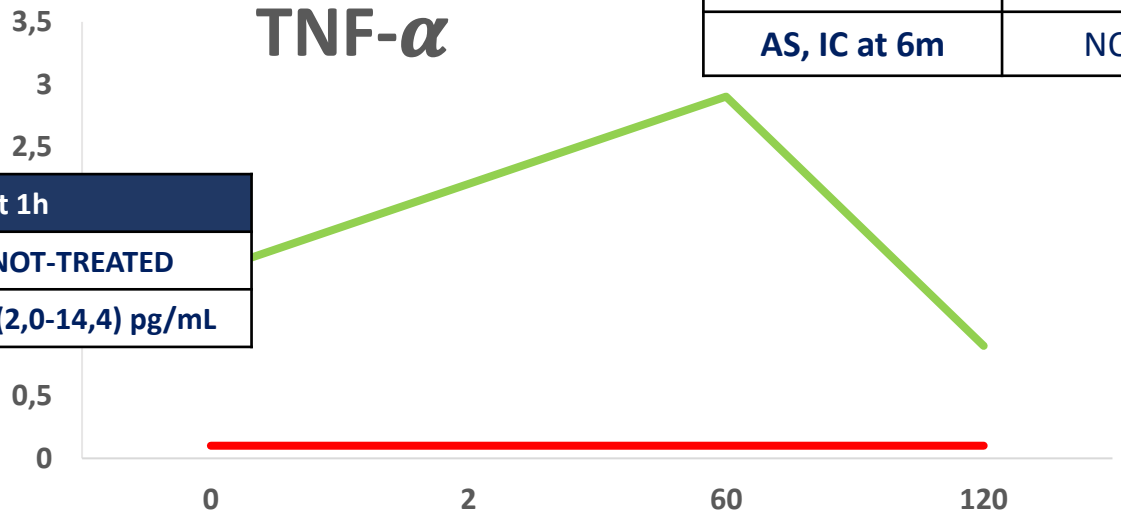


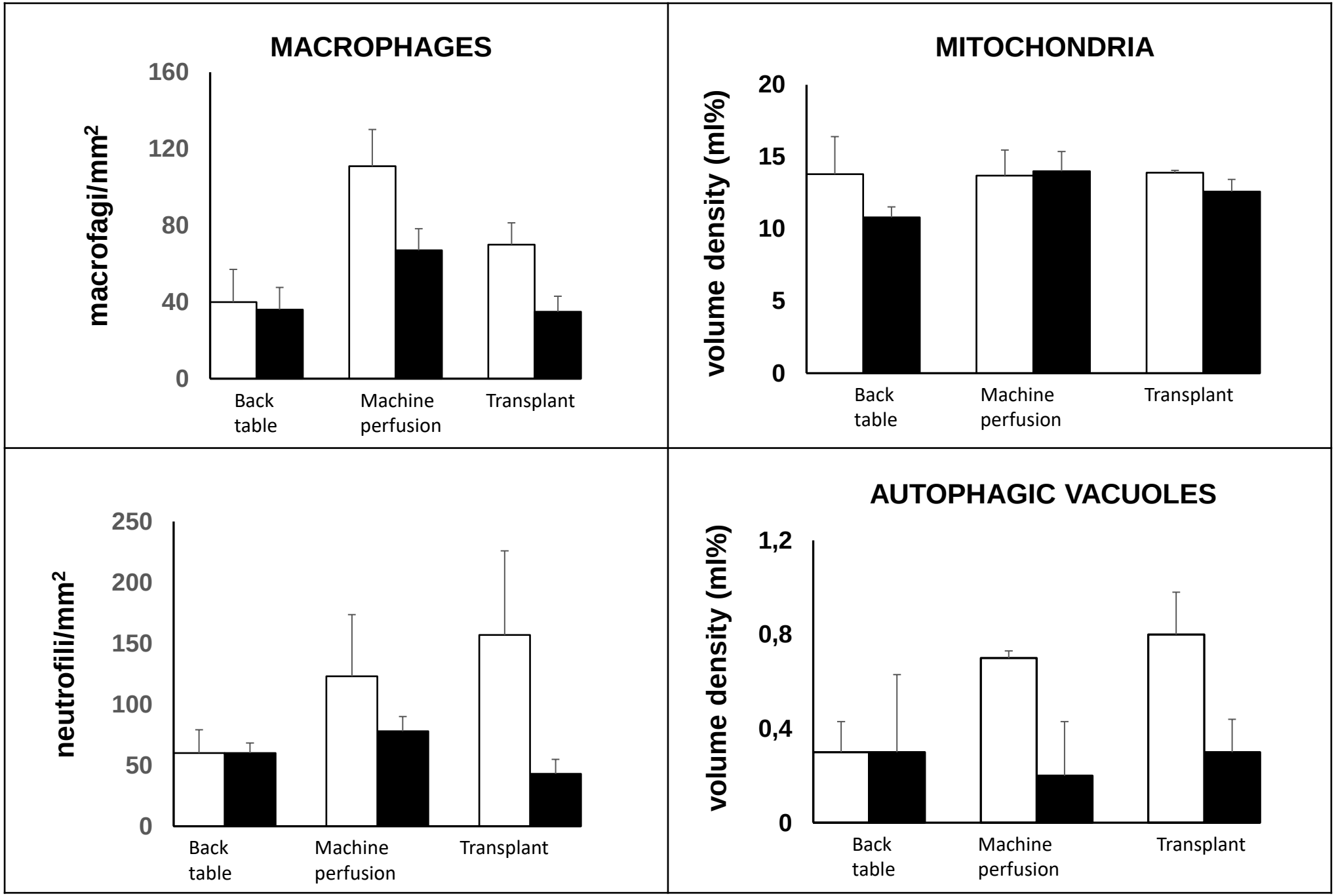
Control Group
CS-Group

POST-TRANSPLANT OUTCOMES		
	TREATED	NOT-TREATED
PRS, EAD	NONE	NONE
ALT peak IU/L	133 (110-218)	137 (129-178)
CCI at discharge	20,9 (0-20,90)	20,9 (0-33,50)
AS, IC at 6m	NONE	NONE

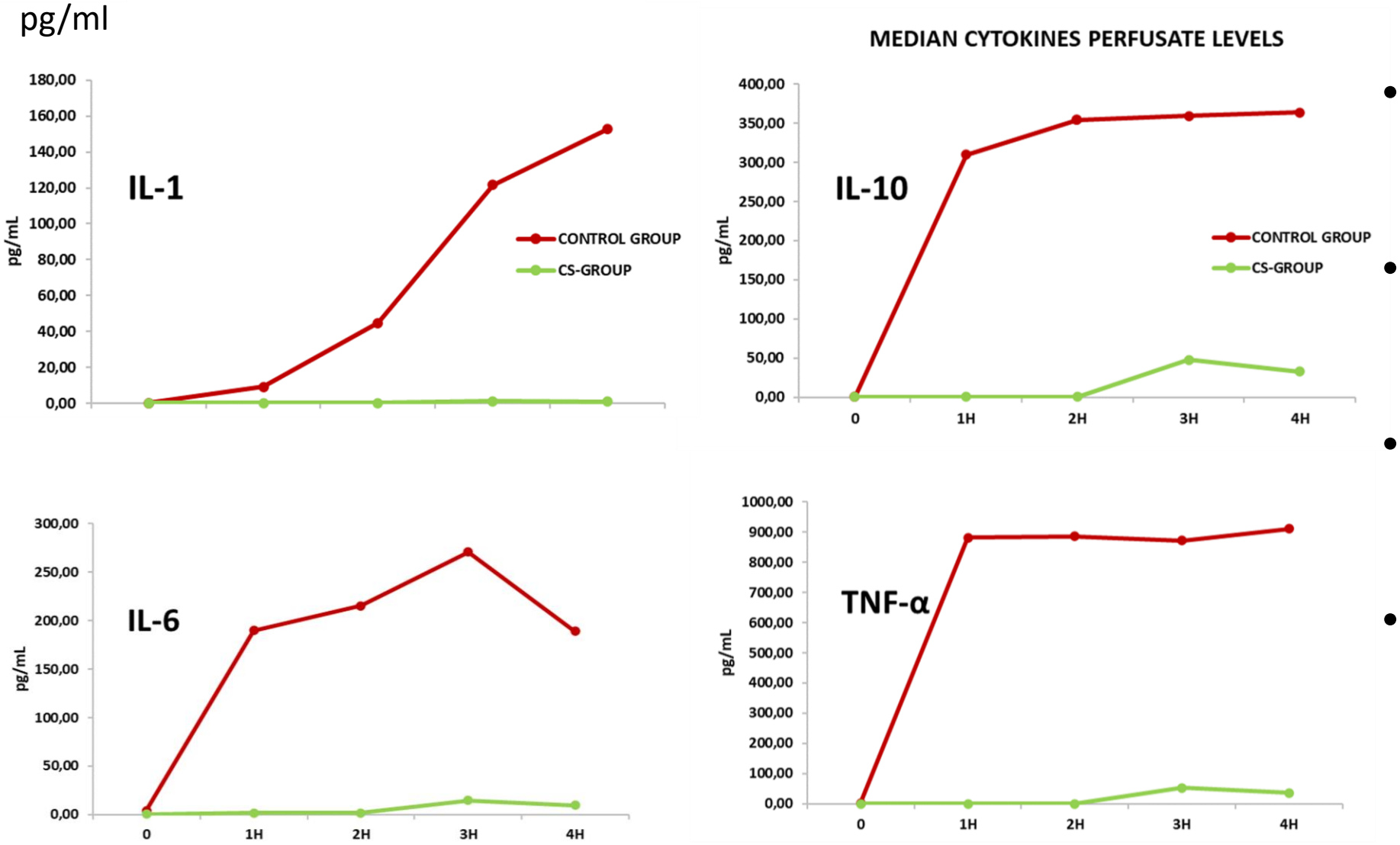


IL-6 (pg/mL) at 1h	
TREATED	NOT-TREATED
2,1 (0,6-4,0) pg/mL	5,4 (2,0-14,4) pg/mL



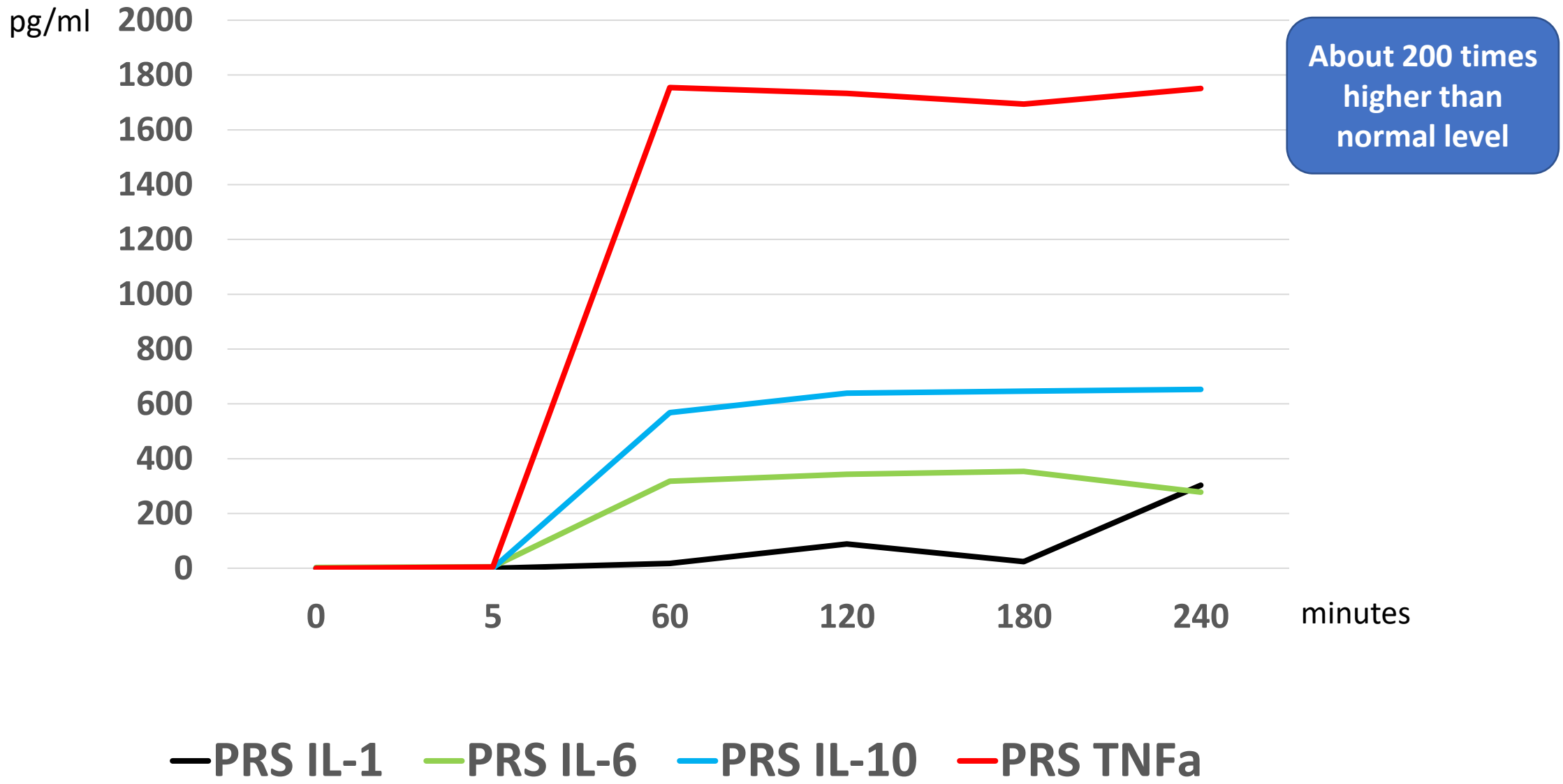

MACROPHAGES
macrofagi/mm2
160
120
80
40
0
Back table
Machine perfusion
Transplant
MITOCHONDRIA
volume density (ml%)
20
15
10
5
0
Back table
Machine perfusion
Transplant
With cytosorb
W/o cytosorb
neutrofili/mm2
250
200
150
100
50
0
Back table
Machine perfusion
Transplant
AUTOPHAGIC VACUOLES
volume density (ml%)
1,2
0,8
0,4
0
Back table
Machine perfusion
Transplant

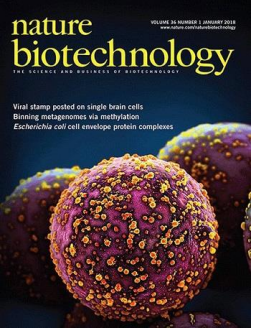
Perfusion liquid purification by cytokine adsorption in liver NMP: promising preliminary results



- One severe PRS in control group
- One case of EAD in the each group
- Lower ICU stay in the CS-Group
- Lower median CCI in the CS-Group (10.45 vs 40.95, p=0.04)

Cytokines during ex-situ NMP: liver graft with severe PRS

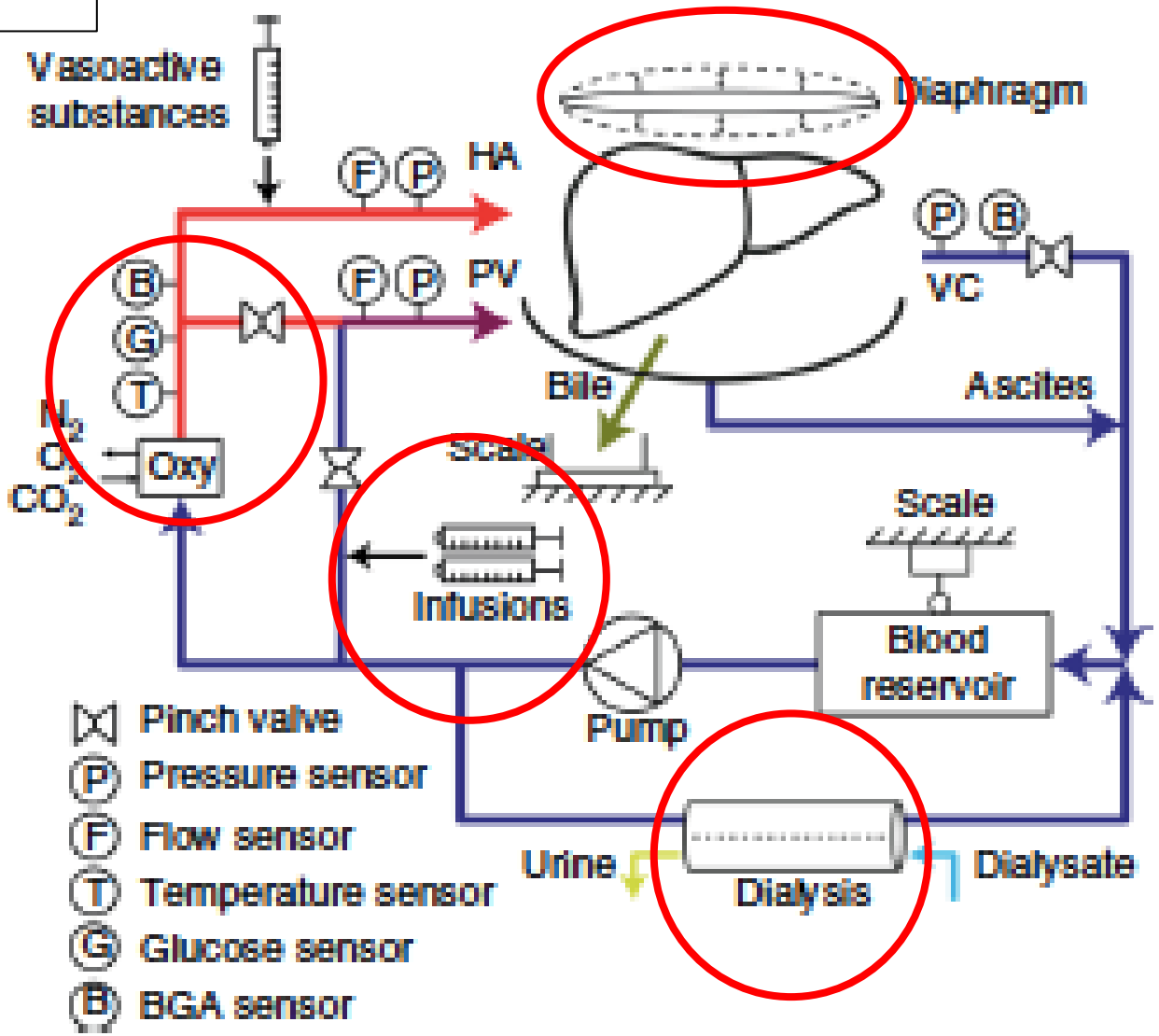


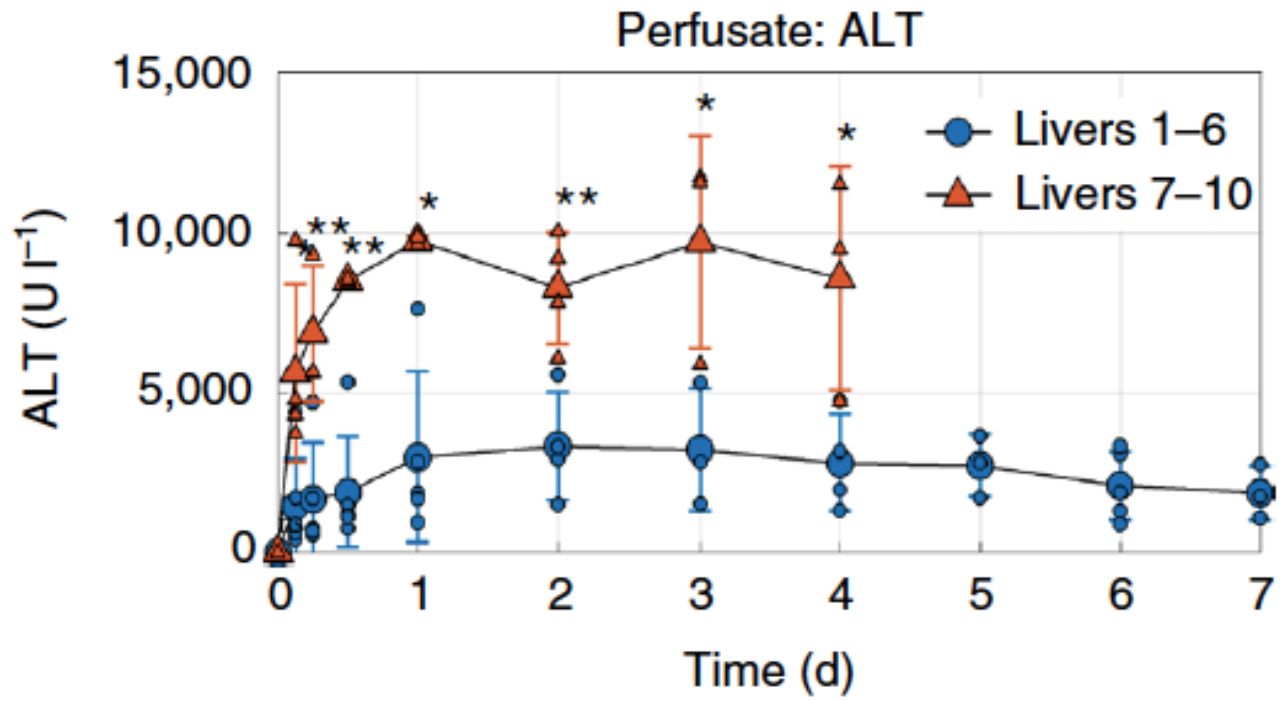


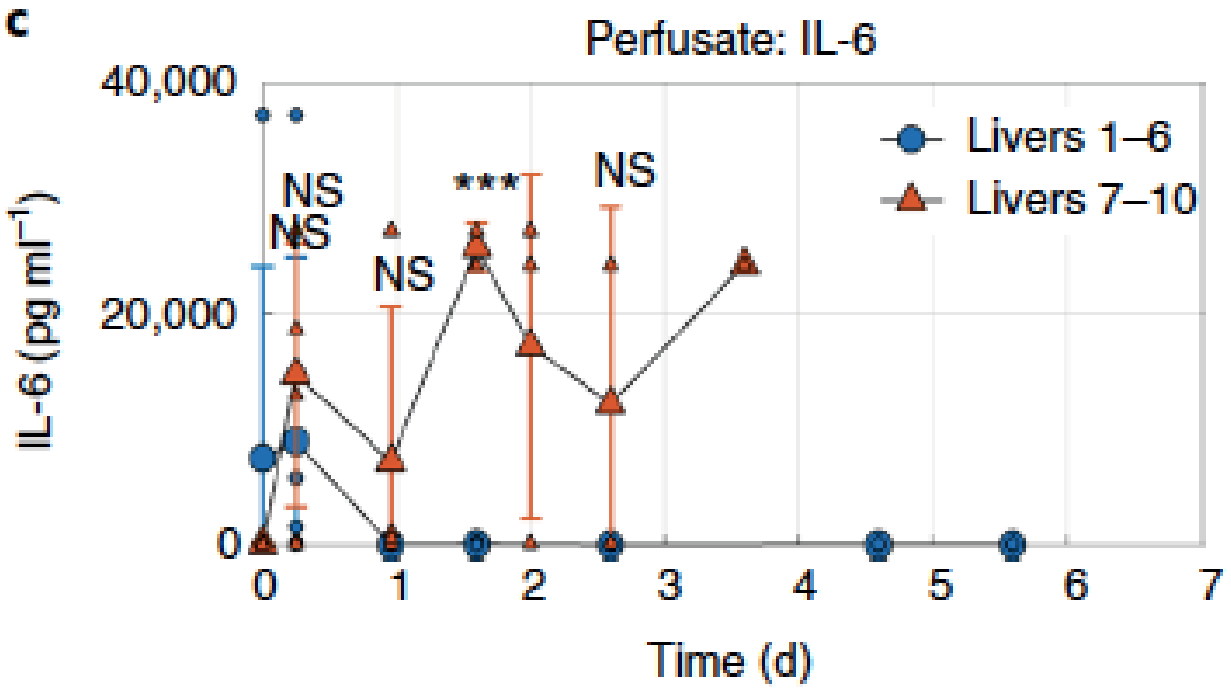
nature biotechnology
ARTICLES
https://doi.org/10.1038/s41587-019-0374-x

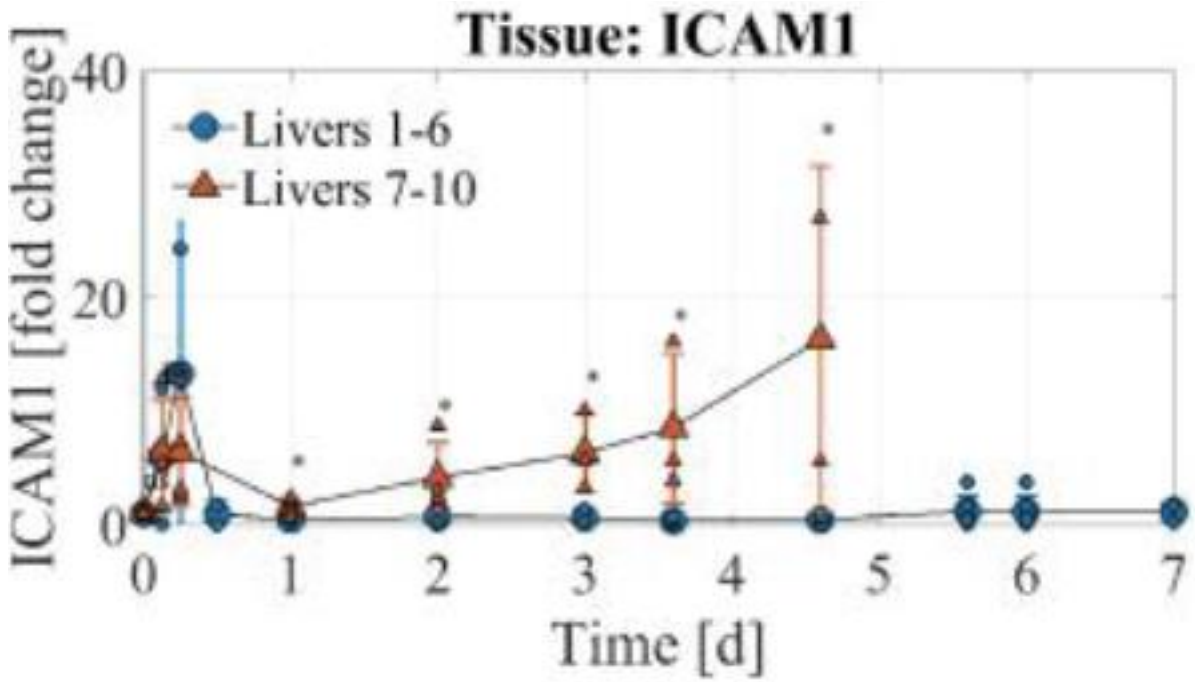
An integrated perfusion machine preserves injured human livers for 1 week

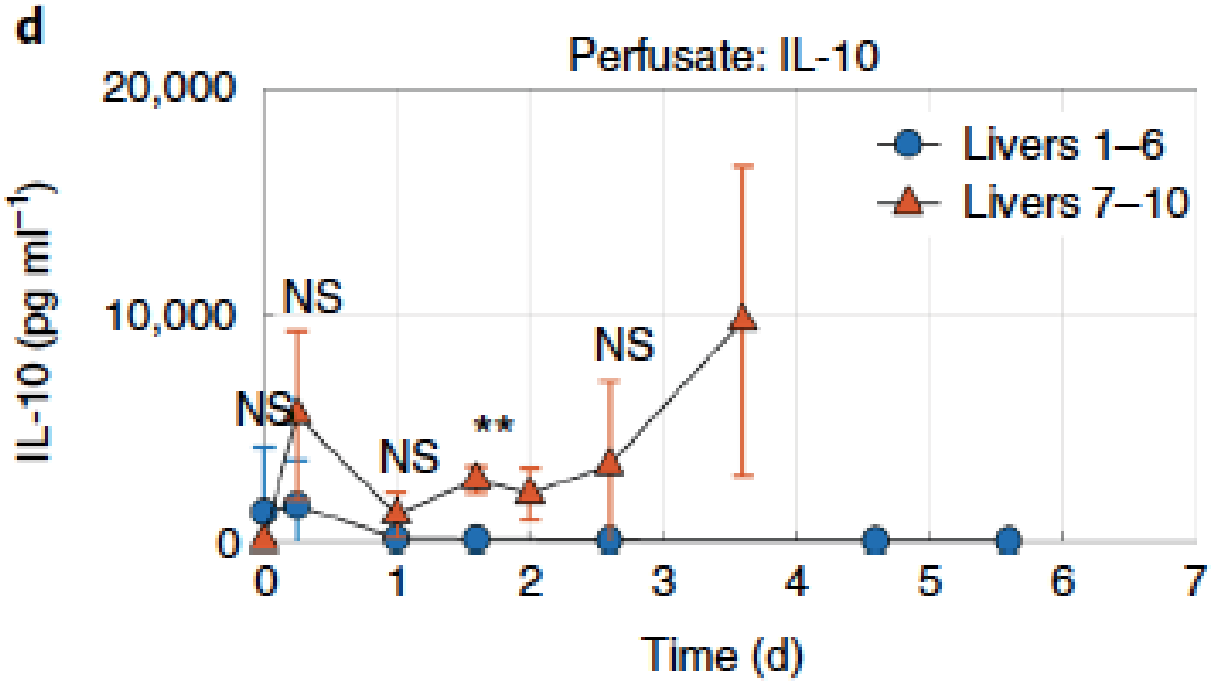
1. Dialysis membrane for waste-product removal
2. Automated control of glucose levels by injection of insulin and glucagon
3. Regulation of oxygenation
4. Liver movement to prevent pressure necrosis

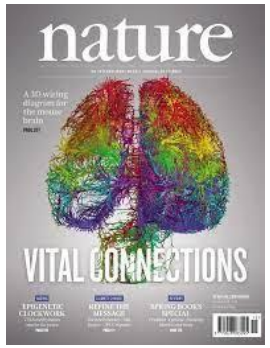



Perfusate: ALT
ALT (U l⁻¹)
15,000
10,000
5,000
0
Livers 1–6
Livers 7–10
**
**
*
**
*
*
0
1
2
3
4
5
6
7
Time (d)


c
Perfusate: IL-6
IL-6 (pg ml⁻¹)
40,000
20,000
0
Livers 1–6
Livers 7–10
NS
NS
NS
***
NS
0
1
2
3
4
5
6
7
Time (d)


Tissue: ICAM1
ICAM1 [fold change]
40
20
0
Livers 1-6
Livers 7-10
0
1
2
3
4
5
6
7
Time [d]

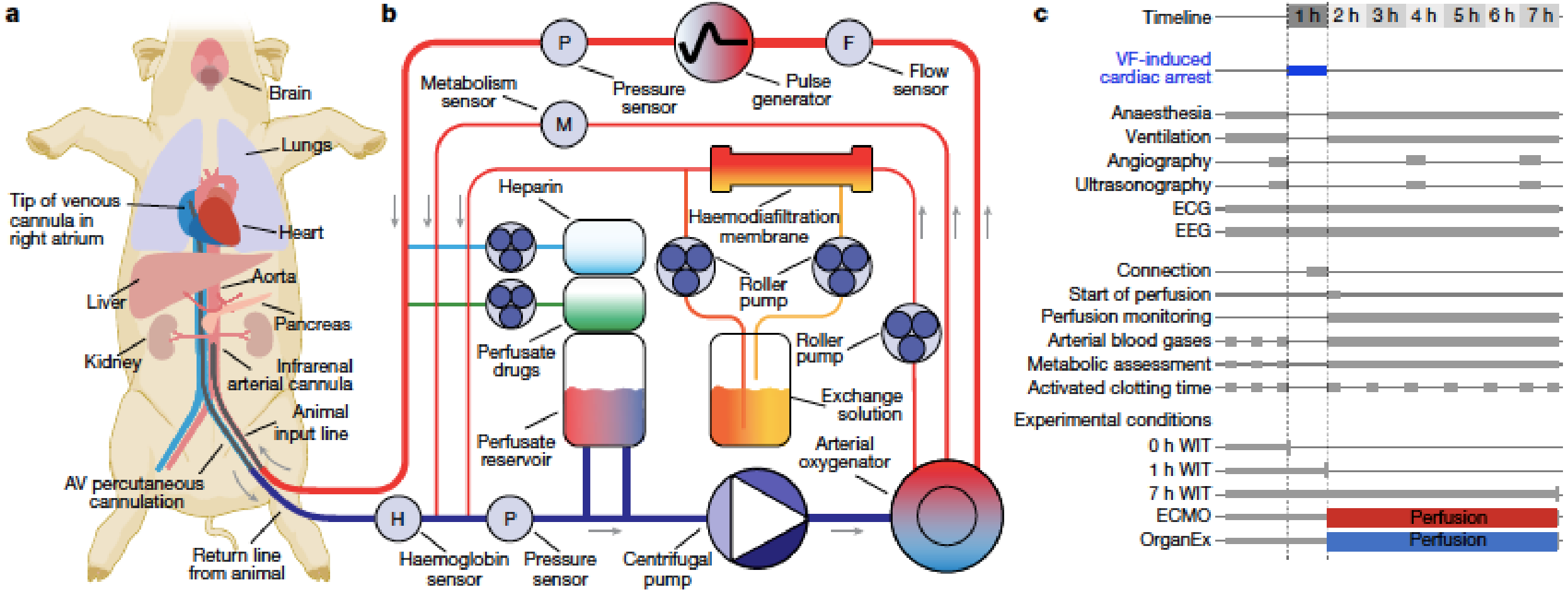

d
Perfusate: IL-10
IL-10 (pg ml⁻¹)
20,000
10,000
0
Livers 1–6
Livers 7–10
NS
NS
NS
**
NS
0
1
2
3
4
5
6
7
Time (d)

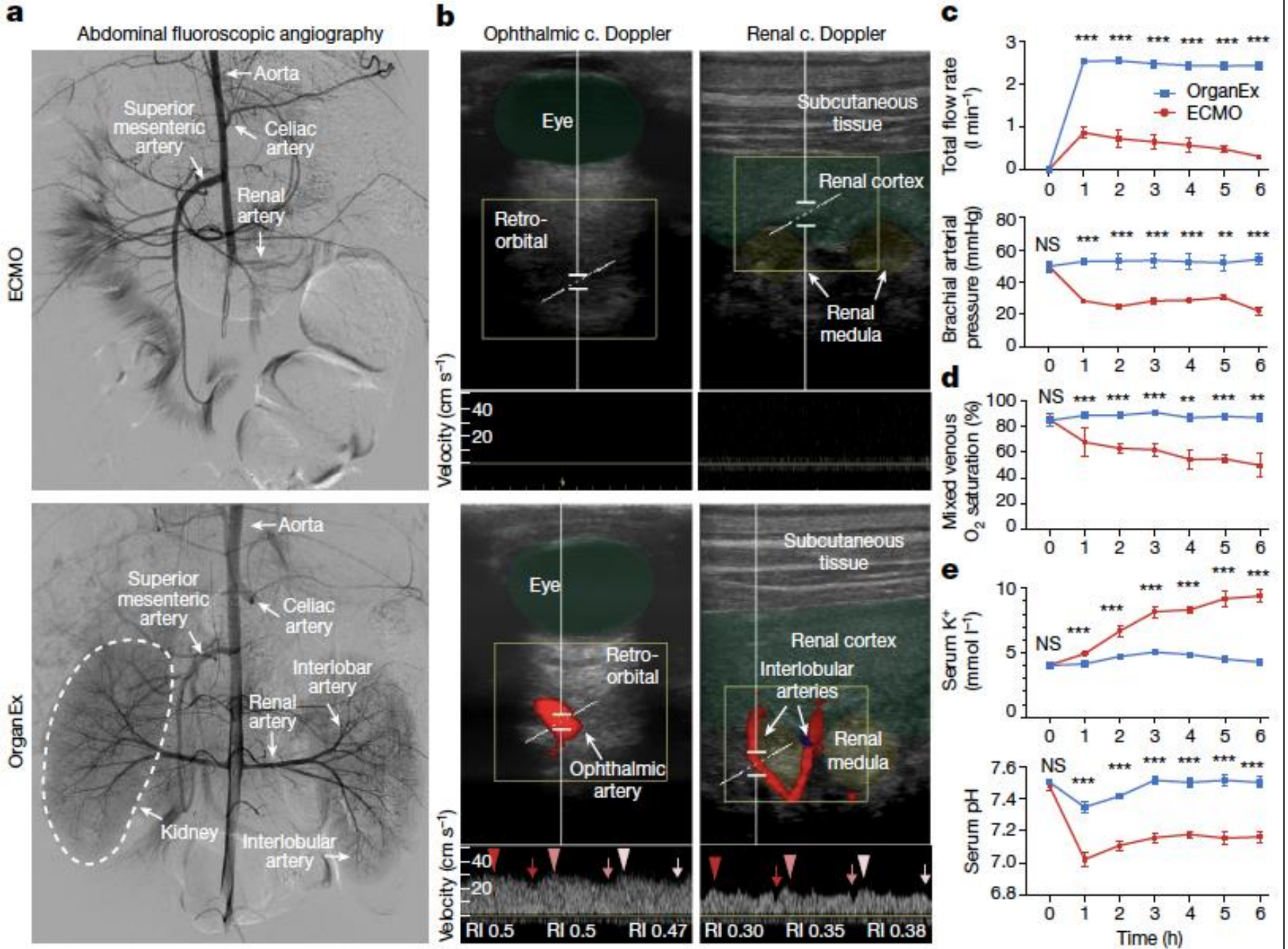


Cellular recovery after prolonged warm ischaemia of the whole body

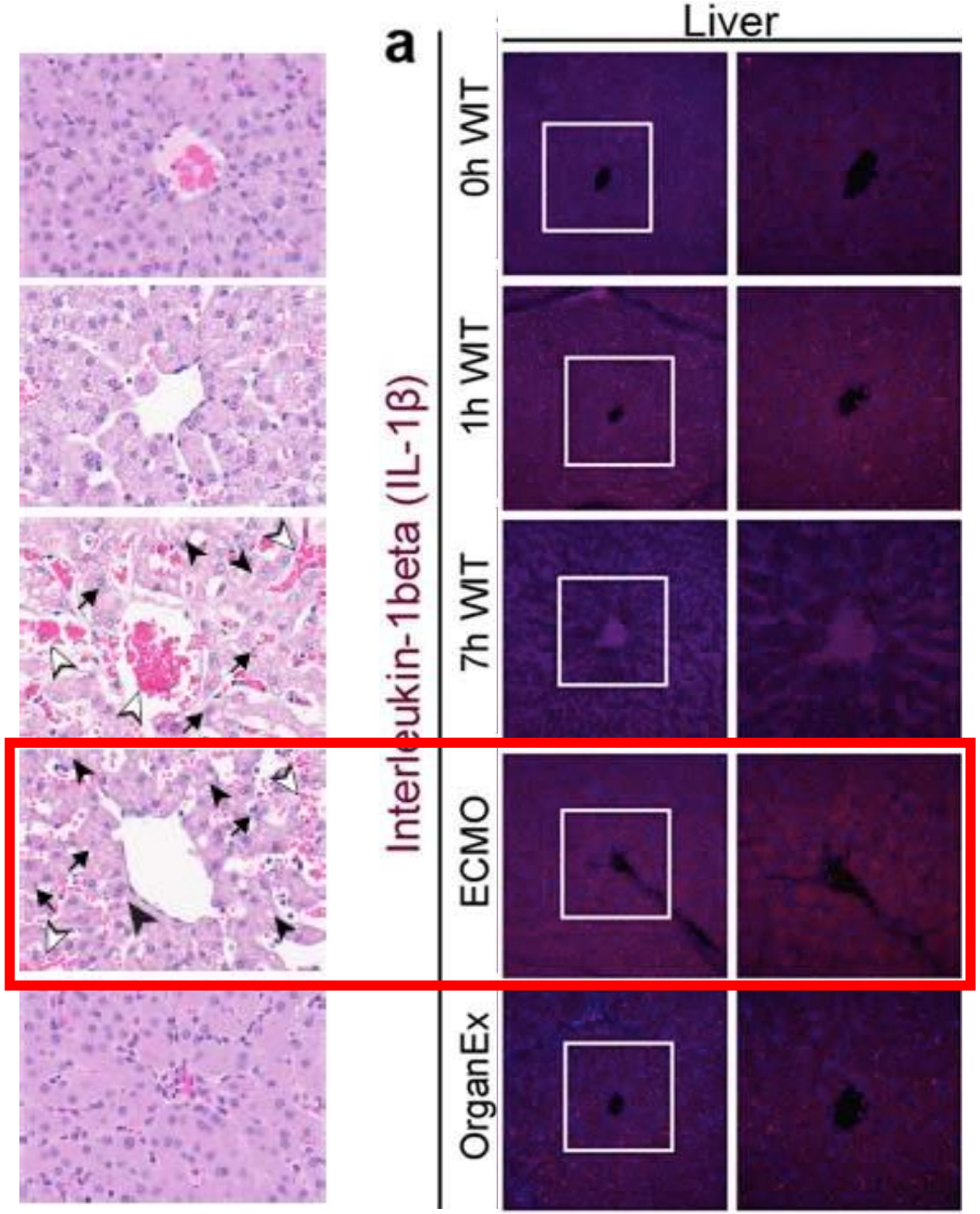
https://doi.org/10.1038/s41586-022-05016-1
Received: 9 September 2021
Accepted: 23 June 2022
Published online: 3 August 2022
Check for updates

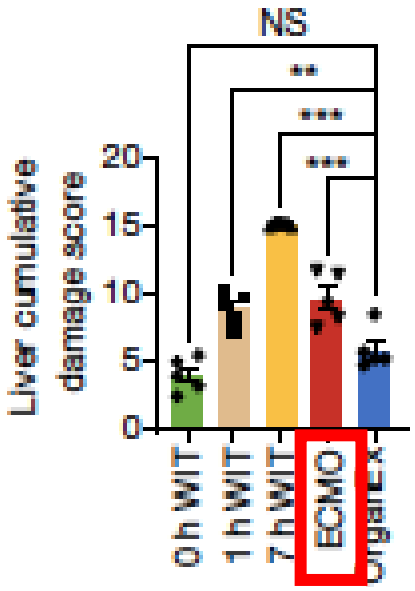
David Andrijevic[1,18], Zvonimir Vrselja[1,18], Taras Lysyy[1,2,18], Shupei Zhang[1,3,18], Mario Skarica[1], Ana Spajic[1], David Dellal[1,4], Stephanie L. Thorn[5], Robert B. Duckrow[6], Shaojie Ma[1], Phan Q. Duy[1,7,8], Atagun U. Isiktas[1], Dan Liang[1], Mingfeng Li[1], Suel-Kee Kim[1], Stefano G. Daniele[1,8], Khadija Banu[9], Sudhir Perincheri[10], Madhav C. Menon[9], Anita Huttner[10], Kevin N. Sheth[6,7], Kevin T. Gobeske[6], Gregory T. Tietjen[2,4], Hitten P. Zaveri[6], Stephen R. Latham[11], Albert J. Sinusas[3,4,12,13] & Nenad Sestan[1,3,14,15,16,17]

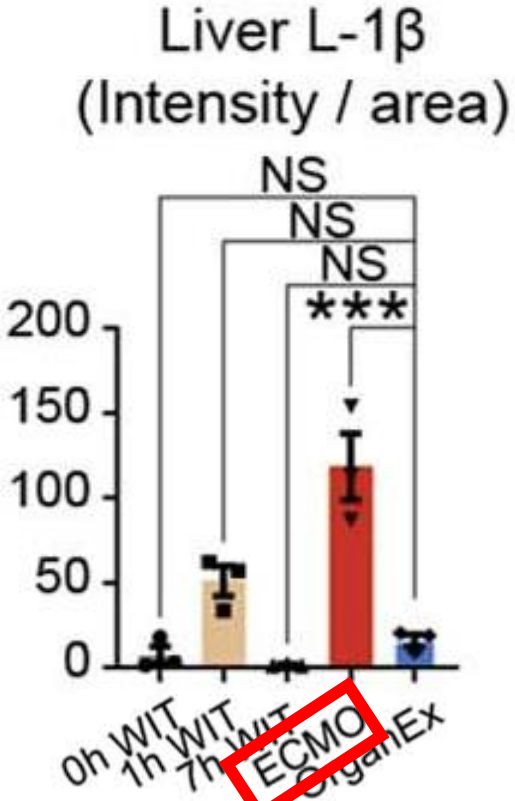




OrganEx technology has the potential to support the recovery of key molecular and cellular processes in multiple porcine organs after 1 hour of global warm ischemia, suggesting that cellular deterioration is a protracted process that can be halted and even shifted versus recovery at a molecular and cellular level







When pyroptosis, the cell death pathway triggered by proinflammatory signals, was investigated with IL-1B immunohistochemistry analysis, liver IL-1B immunolabelling intensity was comparable in the 0, 1, 7h WIT group but increased in the ECMO group compared to OrganEx group

Review of Current Machine Perfusion Therapeutics for Organ Preservation

Jing Xu, BS,[1] Julianna E. Buchwald, BS,[1] and Paulo N. Martins, MD, PhD[1]

Intra-Organ Delivery of Nanotherapeutics for Organ Transplantation

Bilal Hussain,[#] Vivek Kasinath,[#] Joren C. Madsen, Jonathan Bromberg, Stefan G. Tullius, and Reza Abdi*

Extended criteria grafts and emerging therapeutics strategy in liver transplantation. The unstable balance between damage and repair

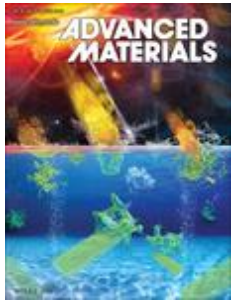
Davide Ghinolfi[a,*], Fabio Melandro[a], Francesco Torri[a], Caterina Martinelli[a], Valentina Cappello[b], Serena Babboni[c], Beatrice Silvestrini[d], Paolo De Simone[a], Giuseppina Basta[c,1], Serena Del Turco[c,*,1]

Machine perfusion therapeutic agents

1) Microcirculation optimizing agents
2) Anti-inflammatory agents
3) Anti-apoptotic agents
4) Defatting agents
5) Mesenchymal stem cells
6) Anti-microorganism agents
7) Free radical scavengers
8) Cellular metabolism optimizers

Study	Animal	Treatment	Treatment category
Nagrath et al[88]	Rat	6 defatting agents[a]	Defatting cocktail
Liu et al[87]	Rat	6 defatting agents[a]	
Hara et al[90]	Rat	Prostaglandin E1	Vasodilator
Maida et al[91]	Rat	Prostaglandin E1	
Nassar et al[92]	Pig	Prostacyclin	
Echeverri et al[89]	Pig	BQ123 and verapamil	
Goldaracena et al[93]	Pig	Antisense oligonucleotide	Gene modulation
Gillooy et al[94]	Rat	siRNA (against Fas)	
Thijssen et al[95]	Rat	siRNA (against p53)	
Goldaracena et al[96]	Pig	Antiinflammatory agents	Other
Rigo et al[97]	Rat	Human liver stem cells extracellular vesicles	
Beal et al[98]	Rat	δ-opioid agonist (enkephalin)	
Yu et al[99]	Pig	NLRP3 inflammasome inhibitor	

[a]The 6 defatting agents used were forskolin, GW7647, scoparone, hypericin, visfatin, and GW501516.
BQ123, an endothelin 1 receptor antagonist; NLRP3, nucleotide-binding domain leucine-rich repeat containing family pyrin domain containing 3.



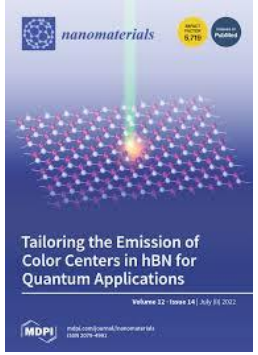
Ceria nanoparticles meet hepatic ischemia-reperfusion injury: the perfect imperfection

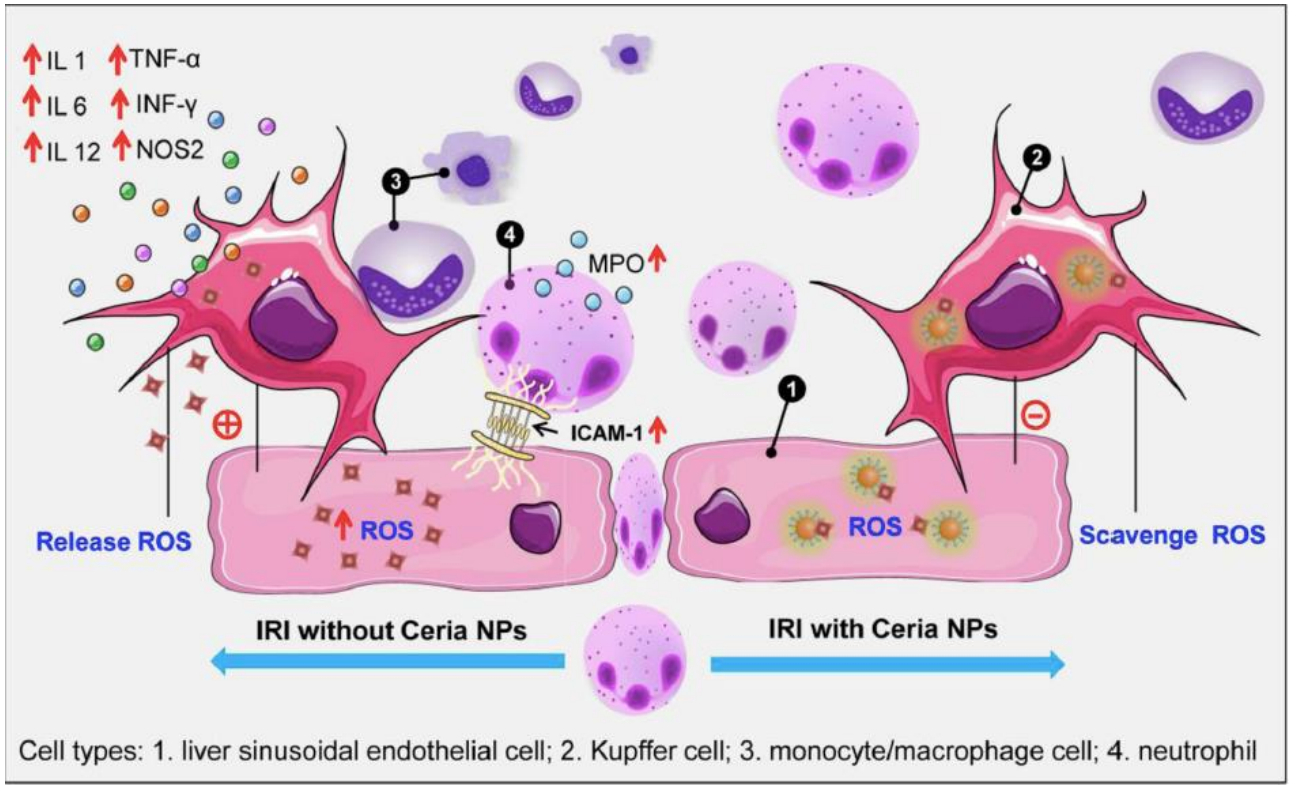
Dalong NI#,
Departments of Radiology and Medical Physics, University of Wisconsin - Madison, Wisconsin 53705, United States

Article

Preparation, Characterization, and Preliminary In Vitro Testing of Nanoceria-Loaded Liposomes

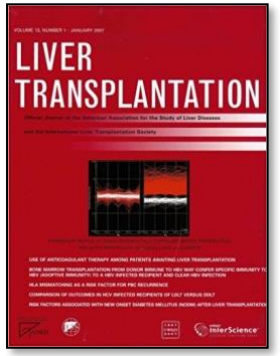
Agostina Grillone [1,*], Tianshu Li [2], Matteo Battaglini [1,3], Alice Scarpellini [4], Mirko Prato [5], Shinji Takeoka [6] and Gianni Ciofani [1,7,*]





CeriaNPs can efficiently scavenge ROS from both intracellular and extracellular sources in the liver.

As the ROS are neutralized, the reduced Kupffer and monocyte/ macrophage cells activation limits the release of pro-inflammatory cytokines, which inhibits the recruitment and infiltration of neutrophils.



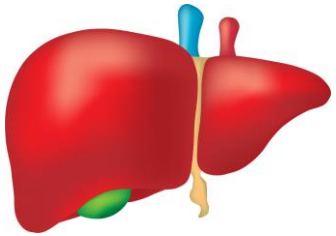
Cerium oxide nanoparticles administration during machine perfusion of discarded human livers: A pilot study

Serena Del Turco[1] | Valentina Cappello[2] | Christos Tapeinos[3] |
Aldo Moscardini[4] | Laura Sabatino[1] | Matteo Battaglini[3] | Fabio Melandro[5] |
Francesco Torri[5] | Caterina Martinelli[5] | Serena Babboni[1] | Beatrice Silvestrini[6] |
Riccardo Morganti[7] | Mauro Gemmi[2] | Paolo De Simone[5] |
Paulo N. Martins[8] | Laura Crocetti[6] | Adriano Peris[9] | Daniela Campani[10] |
Giuseppina Basta[1] | Gianni Ciofani[3] | Davide Ghinolfi[5]

Consiglio Nazionale delle Ricerche

REGIONE TOSCANA

iit ISTITUTO ITALIANO DI TECNOLOGIA



+ Alb-NC (50 µg/mL)

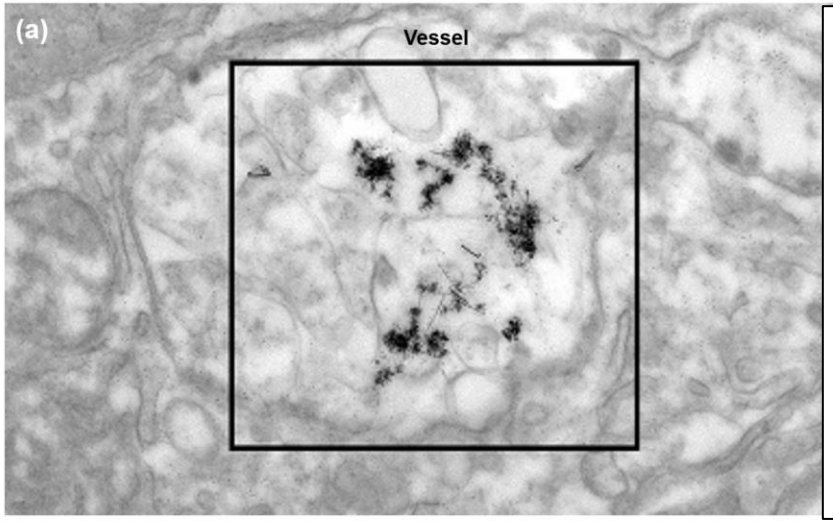
N=5

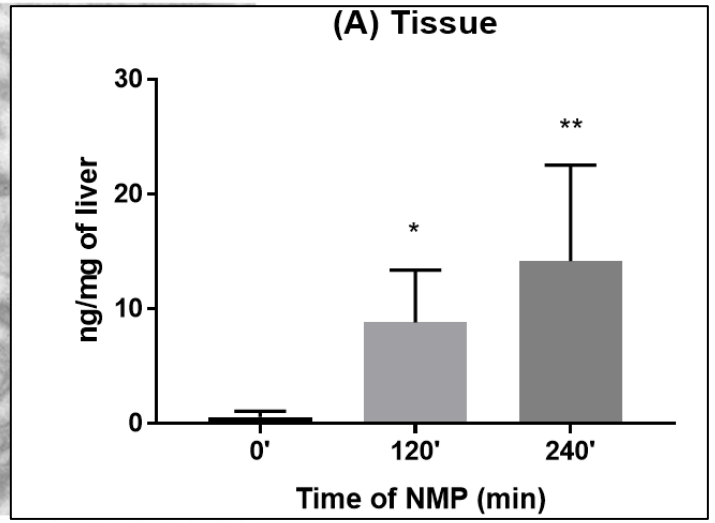
Nothing

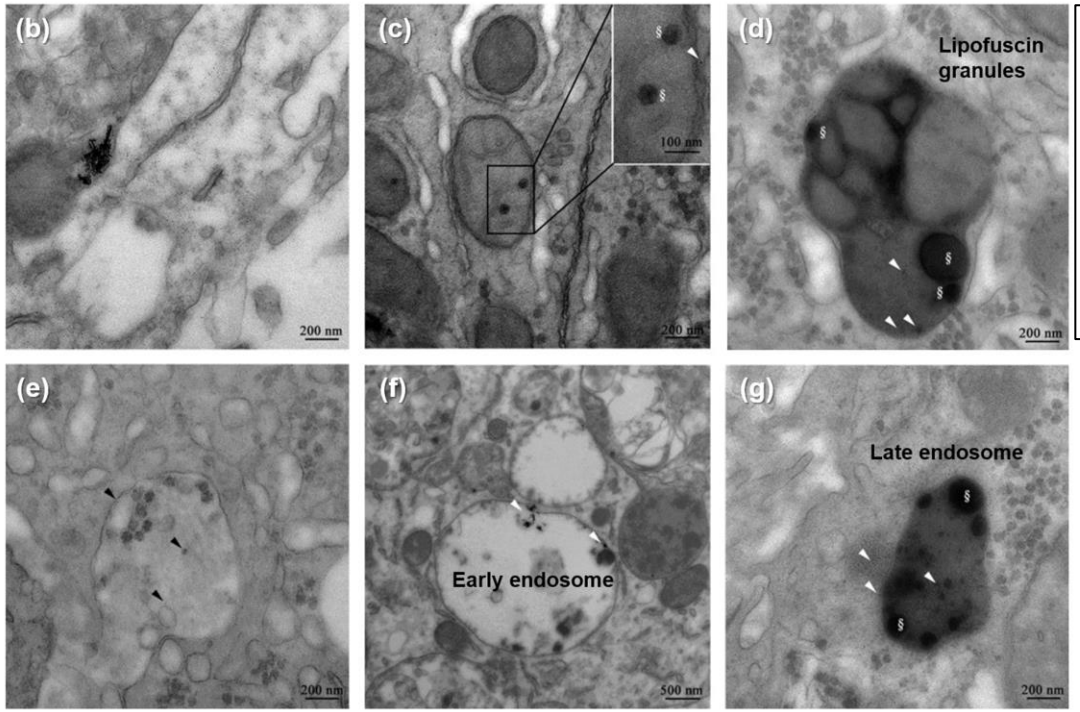
N=4

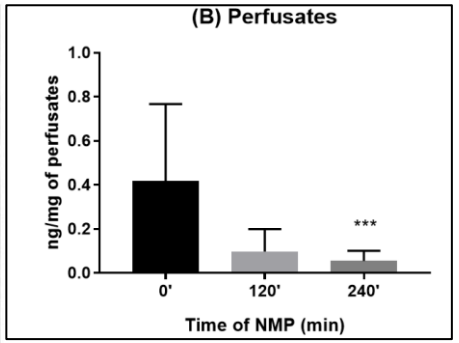
- Primary end point:
  - ✓ to compare antioxidant defenses between two groups (GSH levels, SOD and CAT activity)
- Secondary end point was to evaluate
  - ✓ uptake and distribution of NC
  - ✓ IRI as shown by ultrastructural damages at electron microscopy (lipid droplets, lipofuscin granules, mitochondrial pool)
  - ✓ DNA damages (telomere length and mtDNA4977 deletion)
  - ✓ Changes in pro-inflammatory cytokine expression

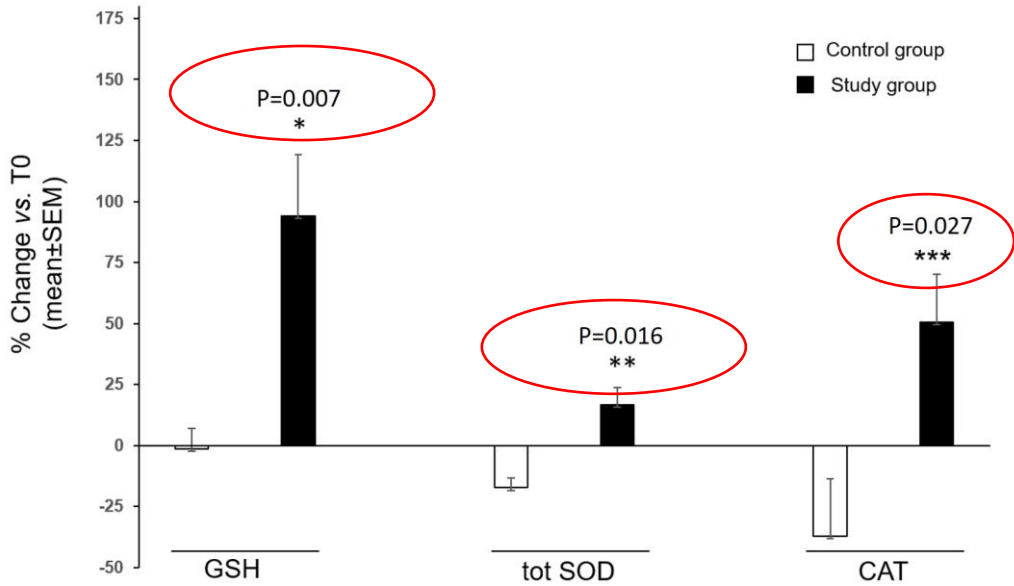
THE EFFECT OF NC ON THE ANTIOXIDANT DEFENSES AND MTDNA

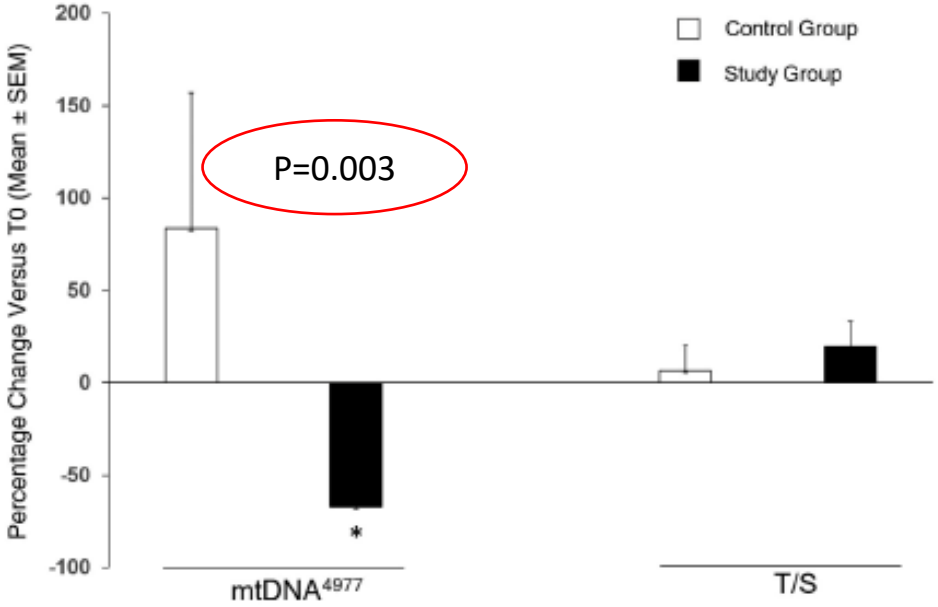


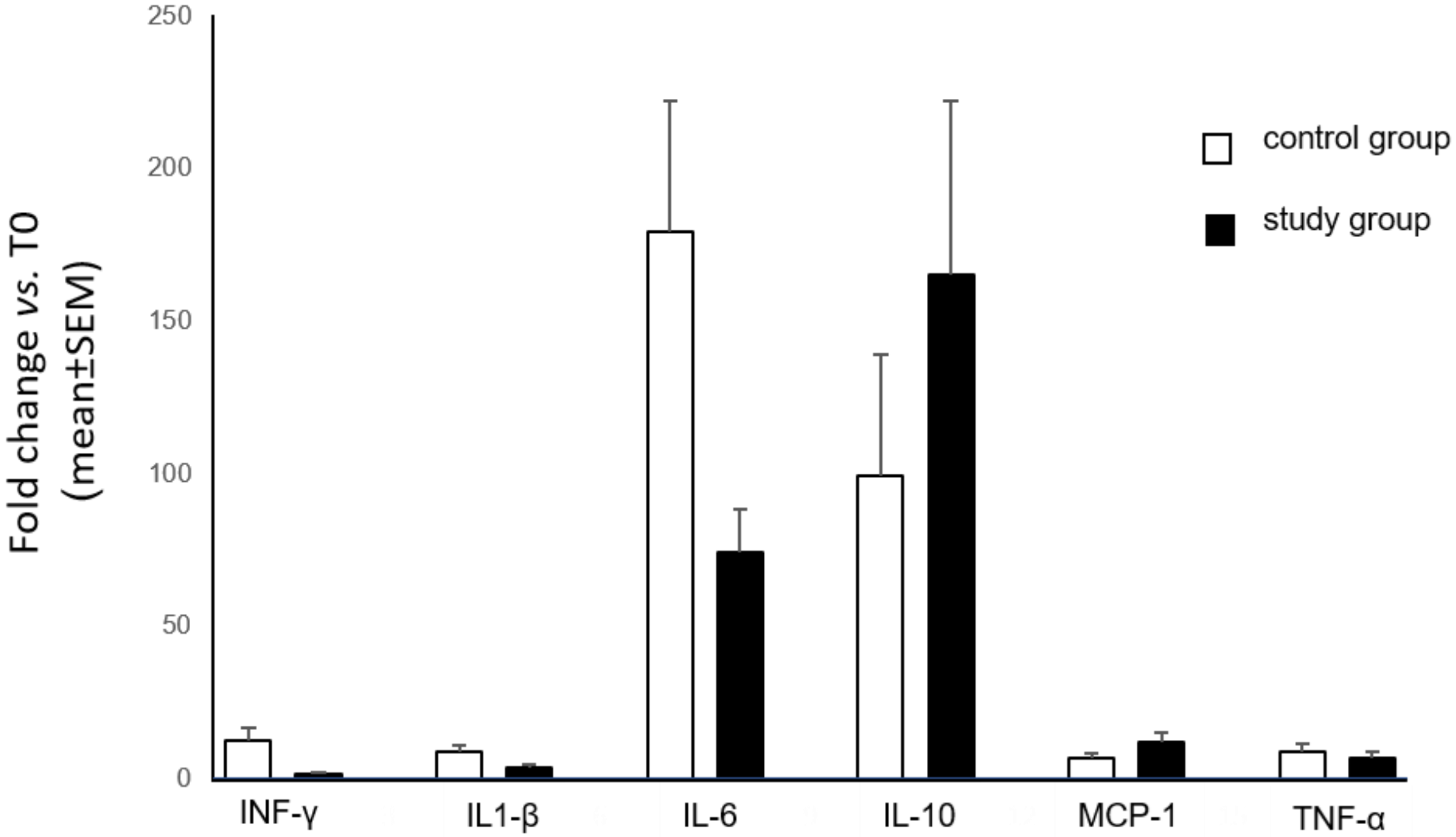











Fold change vs. T0
(mean±SEM)
250
200
150
100
50
0
control group
study group
INF-γ
IL1-β
IL-6
IL-10
MCP-1
TNF-α

Conclusion: the MP revolution just started

- Temperature plays a fundamental role in modulating IRI and inflammatory response during MP
- At the moment, we have no evidence that ILs expression during MP correlates with clinical outcomes
- Perfusate purification and removal of pro-inflammatory cytokines during ex-situ perfusion may have the potential to prevent the cascade of IRI and improve outcomes
- MP are an optimal platform for organ treatment
- MP technology improvement must continues

- *Thank you for your attention !!!*

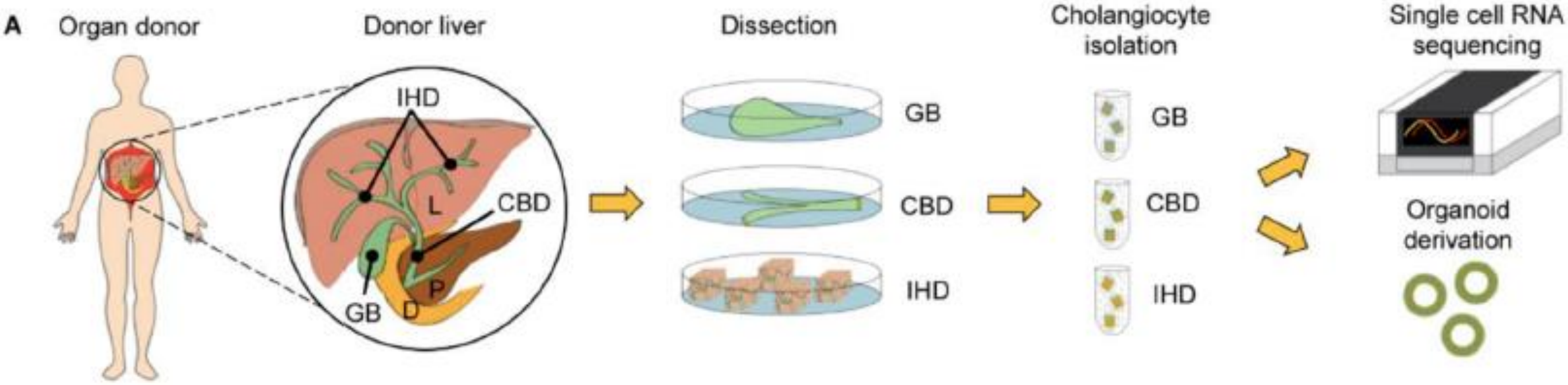
Cholangiocyte organoids can repair bile ducts after transplantation in human liver

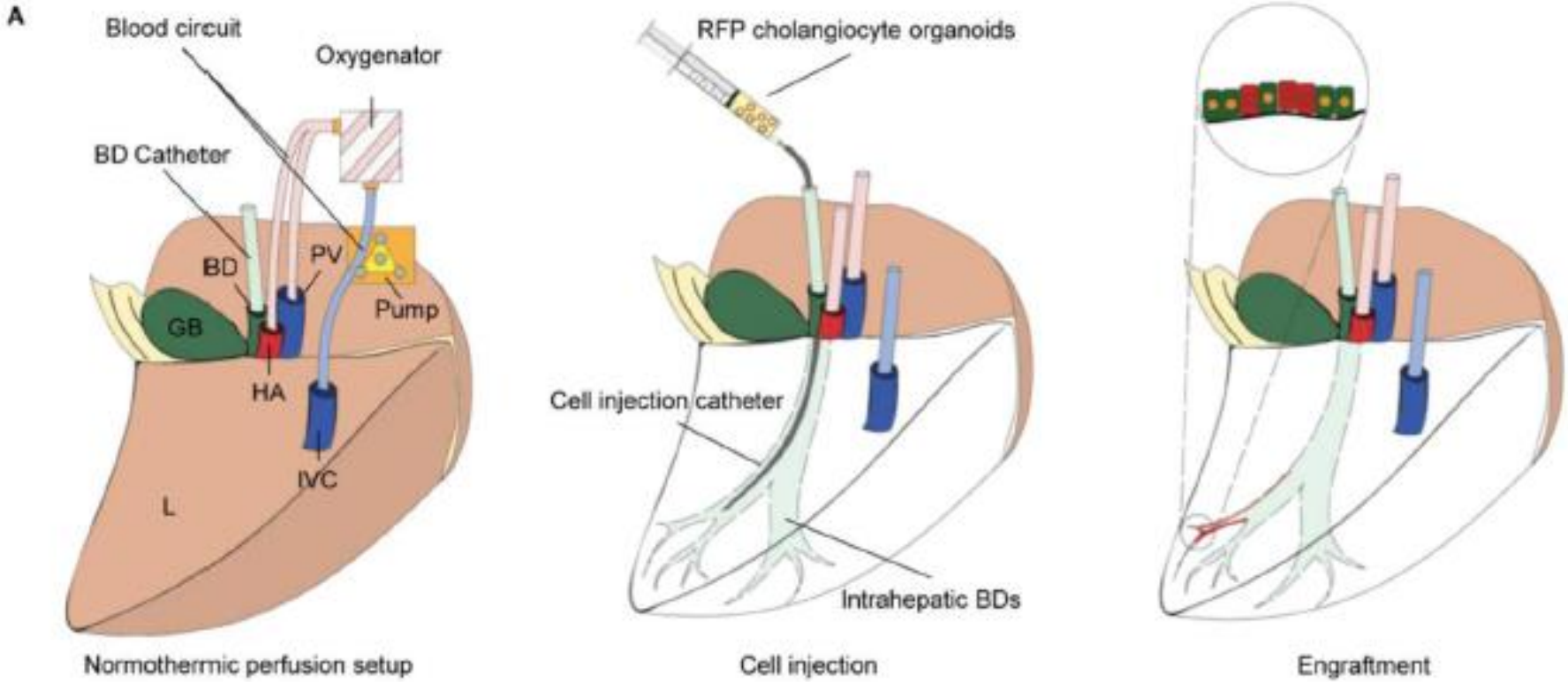
Fotios Sampaziotis[1,2,3,*], Daniele Muraro[1], Olivia C. Tysoe[1,4], Stephen Sawiak[5], Timothy E. Beach[4], Edmund M. Godfrey[6], Sara S. Upponi[6], Teresa Brevini[1], Brandon T. Wesley[1], Jose Garcia-Bernardo[7], Krishnaa Mahbubani[4], Giovanni Canu[1], Richard Gieseck III[8], Natalie L. Berntsen[9,10,11], Victoria L. Mulcahy[2,12], Keziah Crick[13], Corrina Fear[13], Sharayne Robinson[13], Lisa Swift[13], Laure Gambardella[1,2], Johannes Bargehr[1,2,14], Daniel Ortmann[1], Stephanie E. Brown[1], Anna Osnato[1], Michael P. Murphy[15], Gareth Corbett[16], William T. H. Gelson[2,3], George F. Mells[2,3,12], Peter Humphreys[1], Susan E. Davies[17], Irum Amin[4,13], Paul Gibbs[4,13], Sanjay Sinha[1,2], Sarah A. Teichmann[7,18], Andrew J Butler[4,13], Teik Choon See[6], Espen Melum[9,10,11,19,20], Christopher J. E. Watson[4,13,21,22], Kourosh Saeb-Parsy[4,13,†], Ludovic Vallier[1,4,†,*]

Progetto ICOME

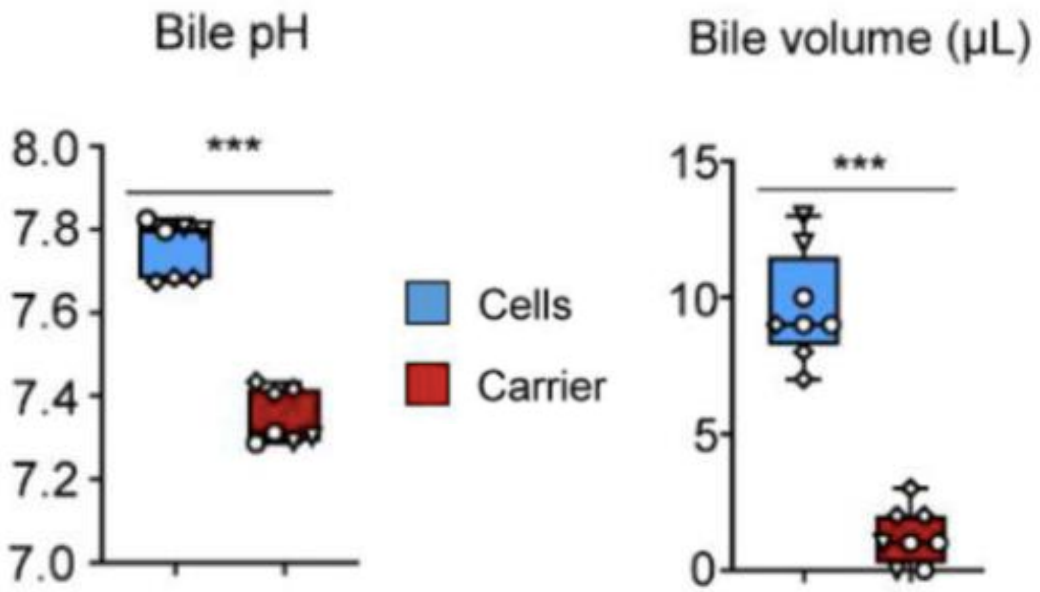
P.I.: D. Ghinolfi

AIRCS ODV
ASSOCIAZIONE ITALIANA RICERCA COLANGITE SCLEROSANTE



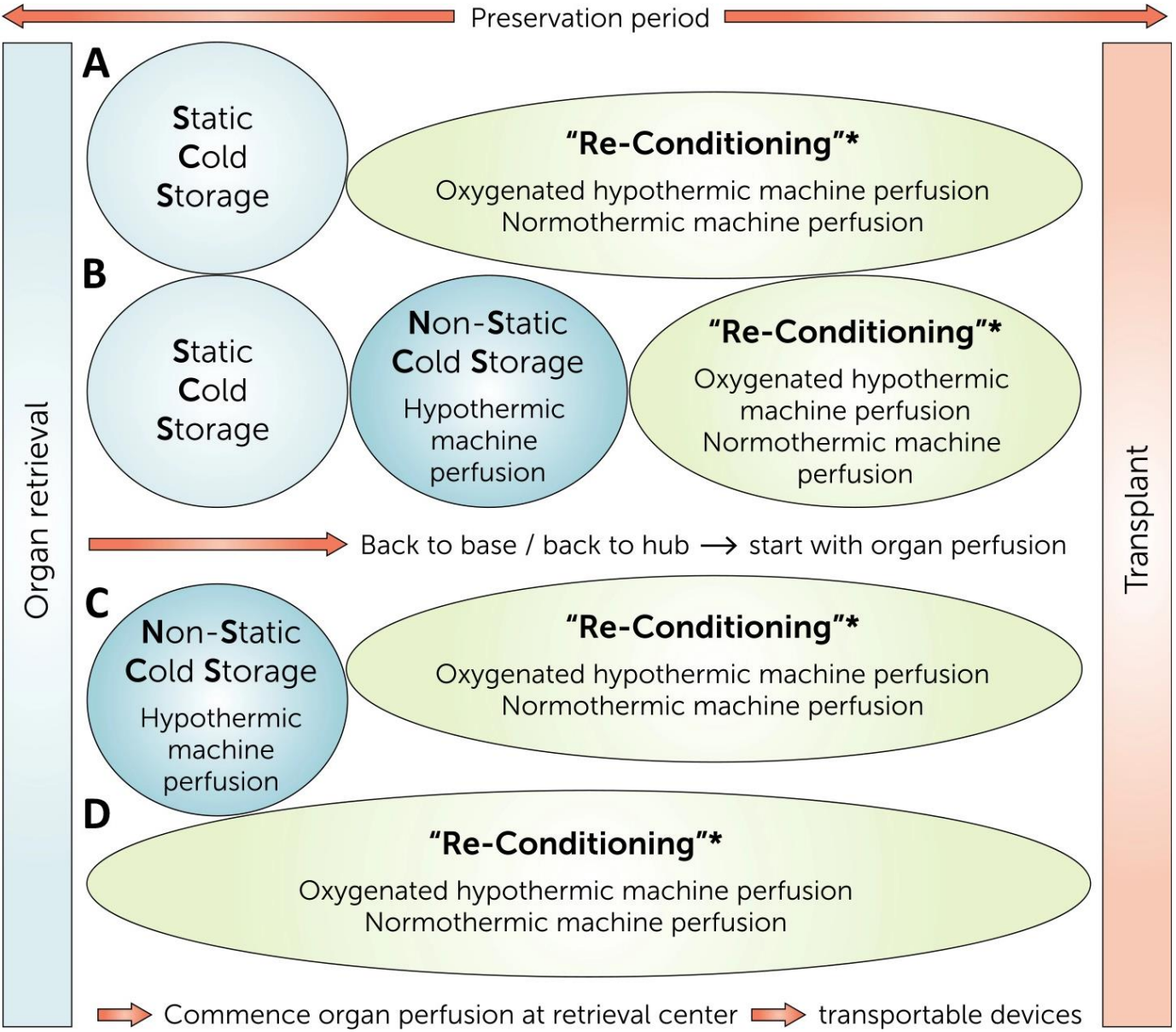

A
Blood circuit
Oxygenator
BD Catheter
BD
PV
Pump
GB
HA
IVC
L
Normothermic perfusion setup
RFP cholangiocyte organoids
Cell injection catheter
Intrahepatic BDs
Cell injection
Engraftment


PRCs
Blood circuit


Bile pH
8.0
7.8
7.6
7.4
7.2
7.0
***
Cells
Carrier
Bile volume (µL)
15
10
5
0
***

Multiple IRI targets lead to different MP approaches: nowadays mainly used as a preservation and evaluation tool

A. Weissenbacher. The future of organ perfusion and reconditioningTransplant International2019; 32: 586–597

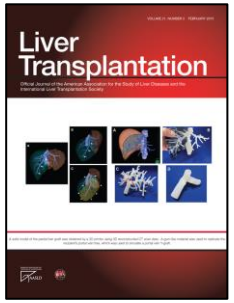


HMP recharges the cellular energy pool through modification of the different complexes in the respiratory chain.

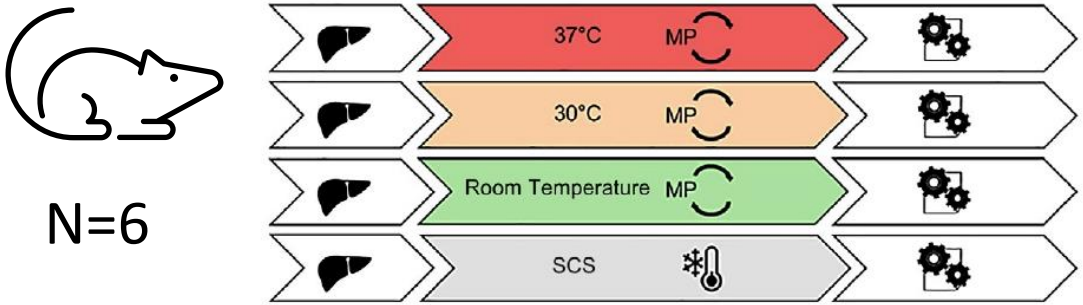
NMP mimics physiological environment, maintains full metabolic activity in the liver, potentially allowing the cellular regenerative process to begin to recover from ischemic damage.

Sequential HMP-COR-NMP allows gentle temperature shift from cold to warm in order to reduce temperature change-induced injury

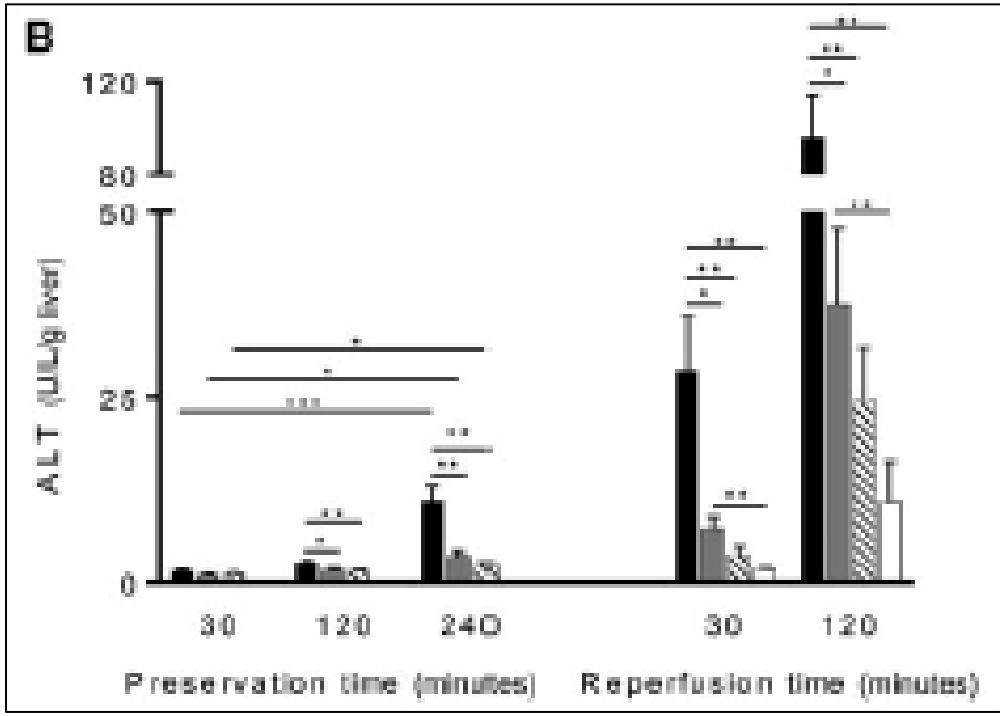
Ischemia-free MP: continuous NMP from the procurement to the transplant

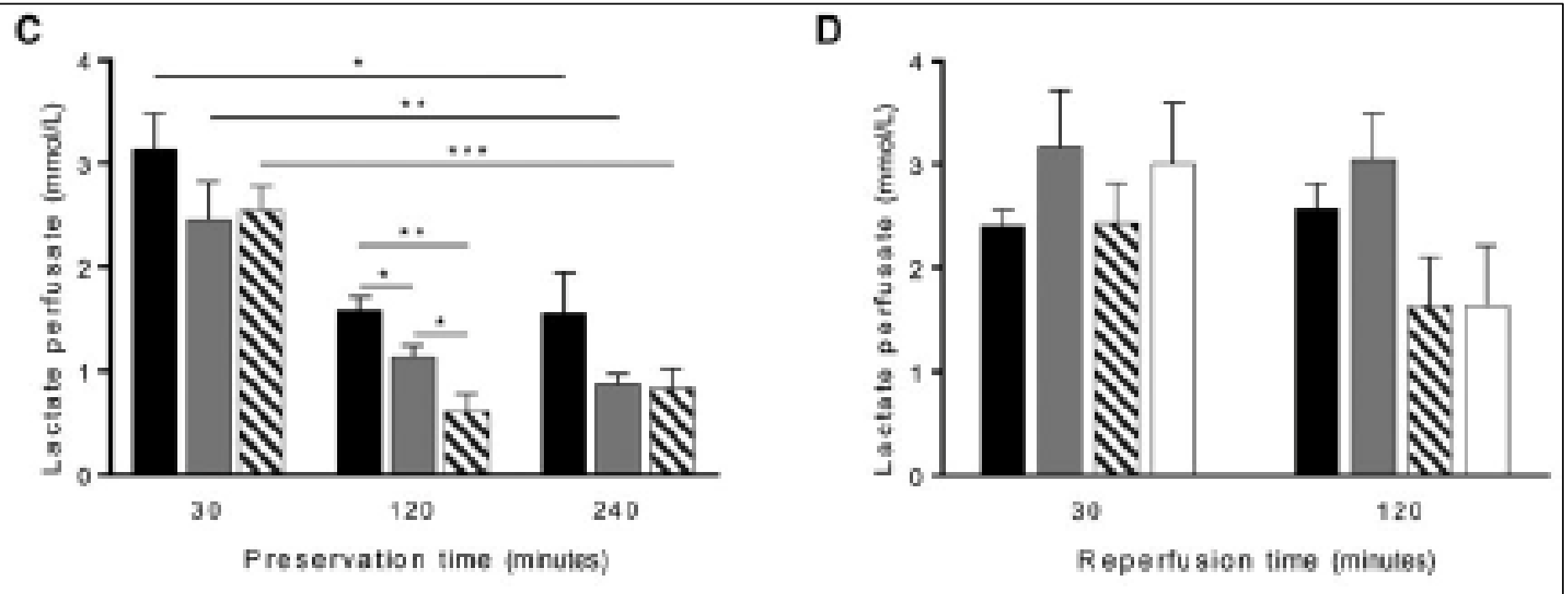


Damage-Associated Molecular Patterns Induce Inflammatory Injury During Machine Preservation of the Liver: Potential Targets to Enhance a Promising Technology

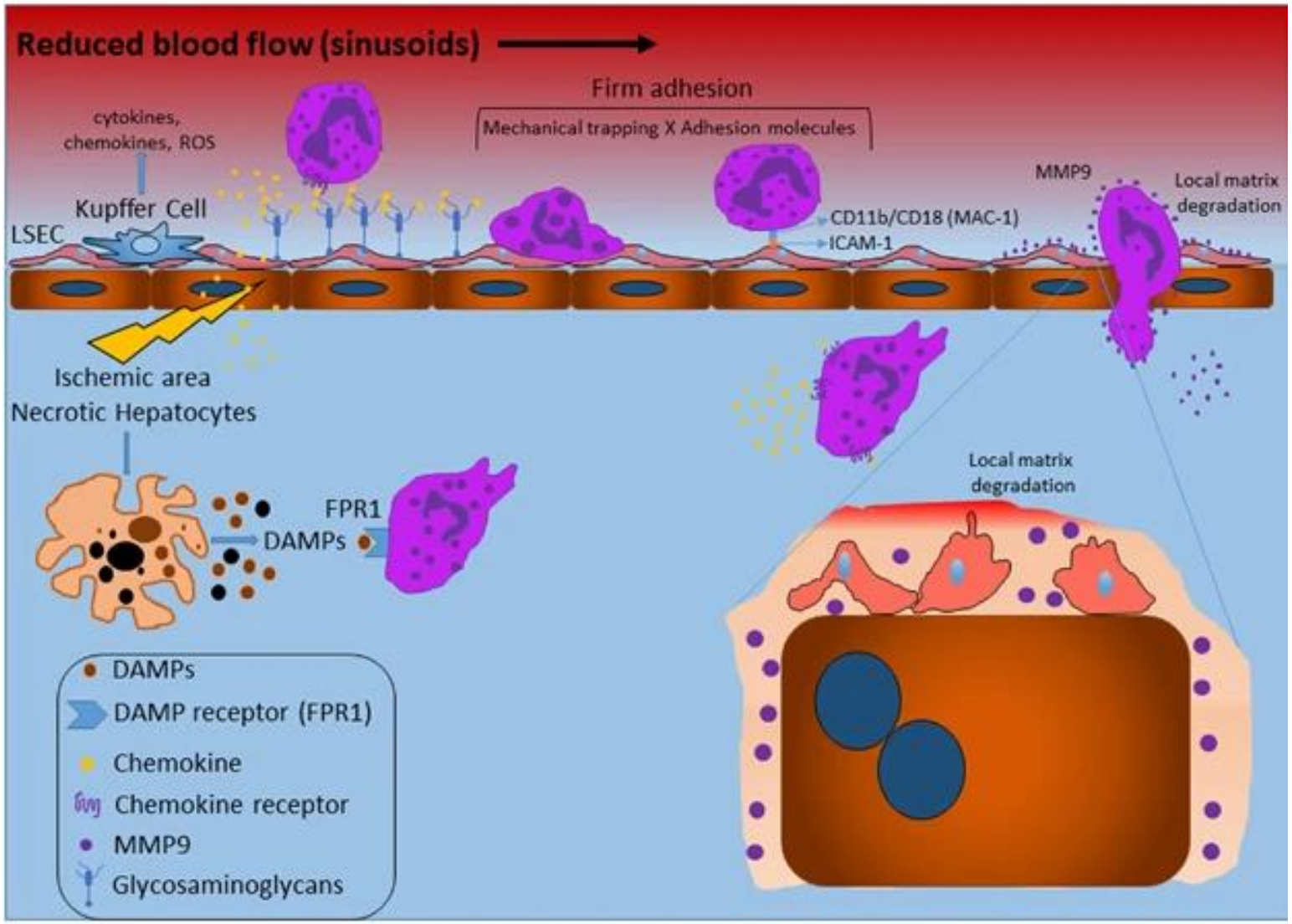


N=6





Liver IRI: the mechanisms



Ischemic cells released **DAMPs**

DAMPs activated **Kupffer cells**

Kupffer generate **pro-inflammatory cytokines and chemokines**

Chemokines guide intravascular neutrophil recruitment

Neutrophil generate firm adhesion

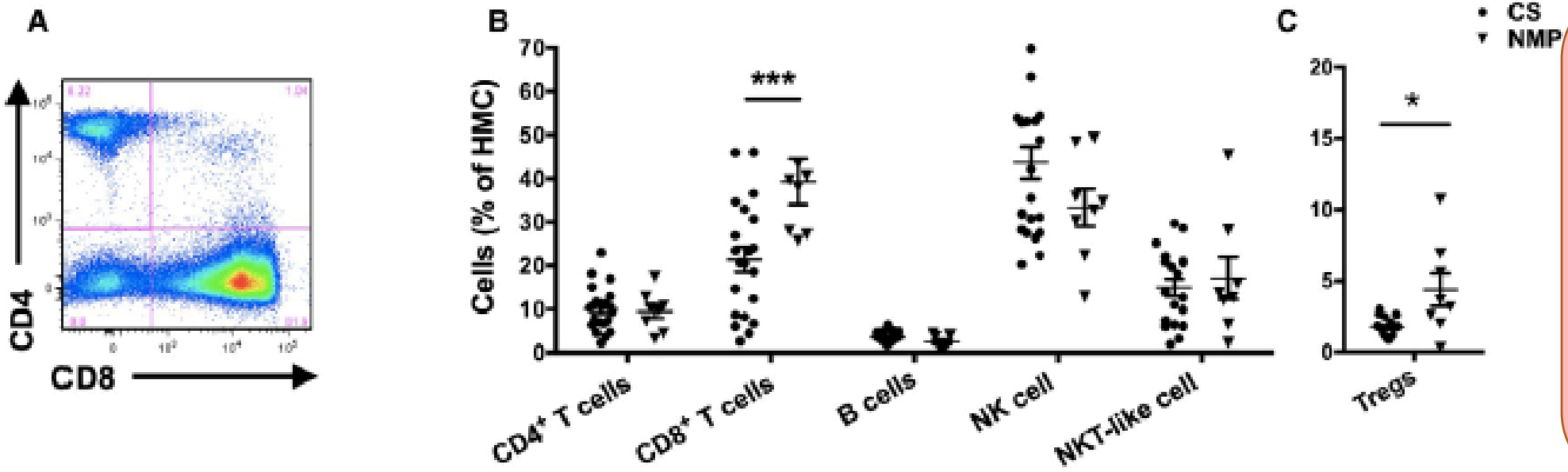
loss of endothelial barrier **integrity**

Liver damage

Oliveira, *et al.* Neutrophils: a cornerstone of liver ischemia and reperfusion injury. *Lab Invest* **98,** 51–62 (2018).

Normothermic Machine Perfusion (NMP) Inhibits Proinflammatory Responses in the Liver and Promotes Regeneration

Wayel Jassem,[1,2] Emmanuel Xystrakis,[1*] Yasmeen G. Ghnewa,[1*] Muhammed Yuksel,[1] Oltin Pop,[1] Marc Martinez-Llordella,[1] Yamen Jabri,[1] Xiaohong Huang,[1] Juan J. Lozano,[3] Alberto Quaglia,[1] Alberto Sanchez-Fueyo,[1] Constantin C. Coussios,[4] Mohamed Rela,[1,2] Peter Friend,[5] Nigel Heaton,[1,2] and Yun Ma[1]



NMP vs SCS

↑ Tregs

↓ $CD4^+$ cells producing IL-4, IL-2, IFN, IL-17