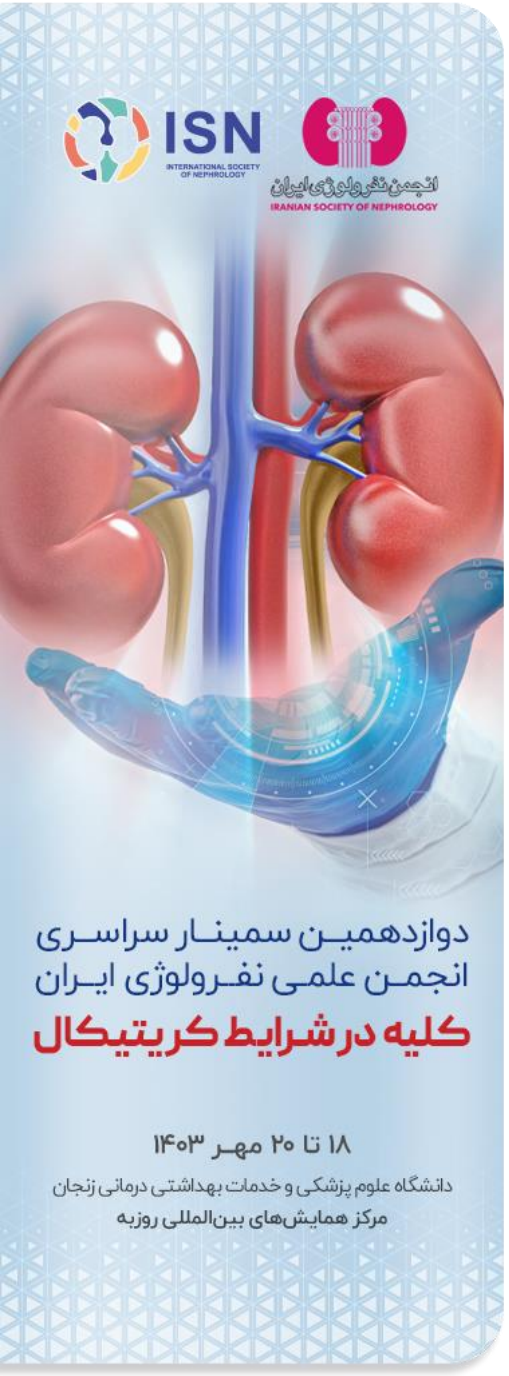


Post kidney Transplantation AKI

Shokoufeh Savaj

Professor of Iran university of medical sciences

INTRODUCTION

- One of the most common complications of kidney transplantation is allograft dysfunction, which in some cases leads to graft loss.
- According to recently published data, AKI affects 30% of kidneys coming from deceased donors and 50% of those coming from deceased donors after cardiac death(DCD)
- Allograft dysfunction is a heterogeneous condition resulting from factors related to procurement, organ quality, recipient medical condition, surgical insult, and graft injury-related to dialysis treatment.

DEFINITION

- Acute allograft dysfunction:

An increase in serum creatinine of ≥25 percent from baseline within a one-to-three-month time period

Failure of the serum creatinine to decrease following transplantation

Proteinuria >1 g/day

- Delayed graft function: the requirement of dialysis sessions in the first week of post-transplantation in a patient who eventually becomes free of dialysis.

Causes Of Acute Allograft Dysfunction

Less than one week

- Postischemic acute tubular necrosis
- Hyperacute rejection
- Volume depletion
- Surgical complications
- Fluid collections
- Atheroemboli
- Calcium oxalate

One week – three months & late (after three months)

- Acute rejection
- Calcineurin inhibitor nephrotoxicity
- Thrombotic microangiopathy
- Recurrent primary disease
- Transplant renal artery stenosis
- Urinary obstruction
- Viral infections
- De novo glomerular disease
- Retained ureteral stent
- Arteriovenous fistulas after kidney allograft biopsy

Risk Factors Of DGF

Donor-Related Risk Factors
AKI and hemodynamic instability in ICU
Prolonged cold ischemia time
Graft quality (old age, CKD risk factors)
Donor type (DCD vs. DBD vs. living donor)
Recipient-Related Risk Factors
Surgery
Complex vascular surgery/vascular complications (prolonged warm ischemia time)
Increased BMI, concomitant surgery (e.g., ADPKD nephrectomy)
High immunological risk/rejection
Pre-transplantation oliguria (HD vs. PD; long dialysis vintage vs. pre-emptive)
Pre-transplantation HD/UF session
Perioperative Risk Factors
Peri-operative hypotension/hypovolemia
High CNI blood levels

BIOMARKERS OF DGF

Predictive donor biomarkers

- Donor plasma mitochondrial DNA levels
- Donor urinary C5a levels
- Matrix metalloproteinase-2 levels,
- Periredoxin-2 and periredoxin-1
- Antitrypsin, and exosomal neutrophil gelatinase associated lipocalin (NGAL)

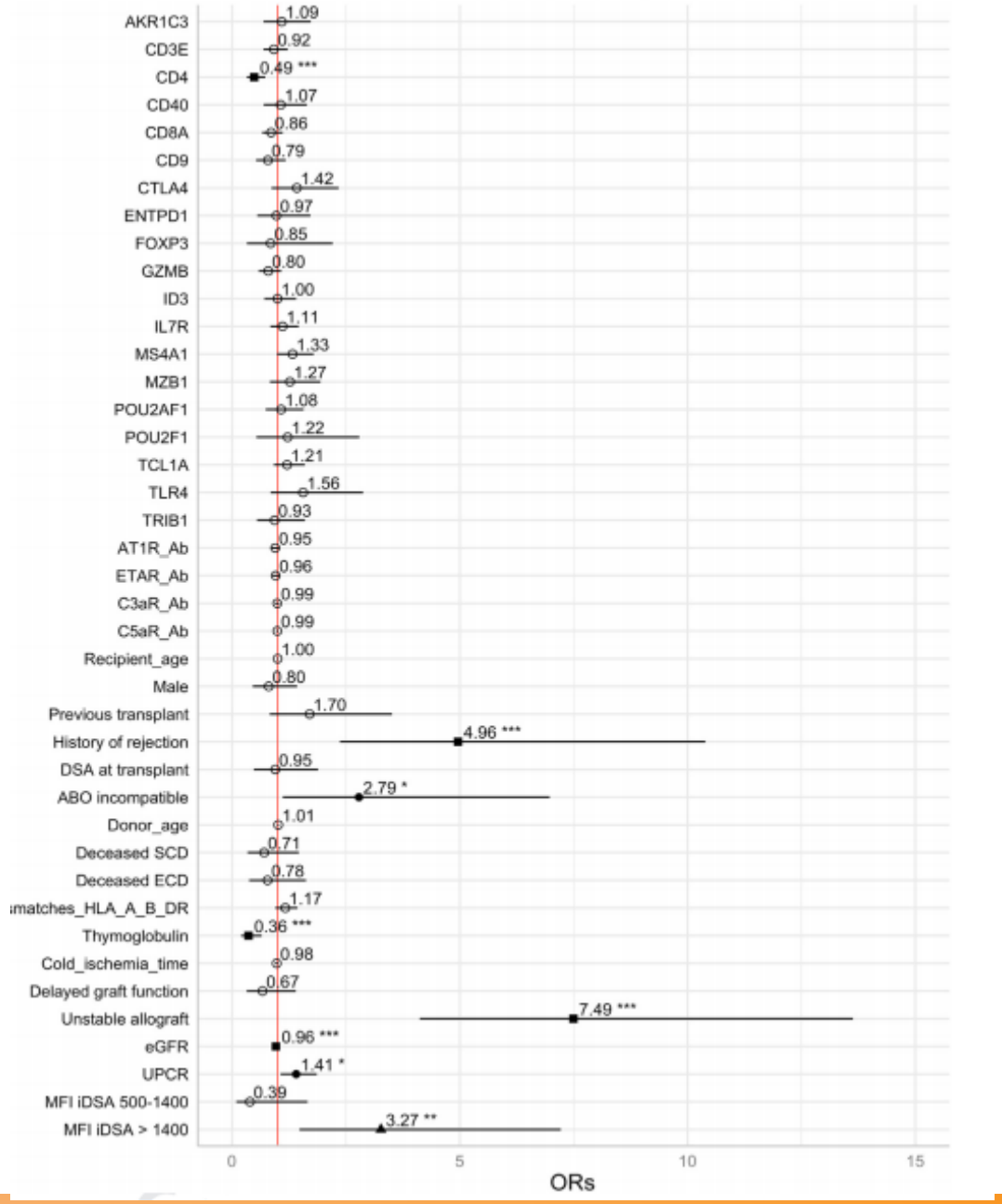
Predictive Recipient biomarkers

- Cell-free microRNAs (miRNAs)
- Short non-coding RNAs
- miR-505-3p
- LDH and NGAL
- Vimentin and fascin
- Plasma endothelial extracellular
- vesicles

Evaluation Of Non-invasive Biomarkers Of Kidney allograft Rejection In A Prospective Multicenter unselected Cohort Study (EU-TRAIN)

- We designed the **European TRAnsplantation and Innovation** (EU-TRAIN) study (ClinicalTrials.gov, NCT03652402) to assess 19 blood mRNAs and 4 non-HLA antibodies in consecutive deeply phenotyped adult patients who received a kidney allograft between November 2018 and June 2020 in 9 European transplant institutions.
- The blood messenger RNAs and non HLA antibodies did not show an additional value beyond standard of care monitoring parameters and circulating anti-HLA DSA to predict allograft rejection in the first year post-transplantation.

All other tested biomarkers, including AKR1C3, CD3E, CD40,CD8A, CD9, CTLA4, ENTPD1, FOXP3, GZMB, ID3, IL7R,MS4A1, MZB1, POU2AF1, POU2F1, TCL1A, TLR4,andTRIB1,as well as antibodies against angiotensin II type 1receptor, endothelin 1 type A receptor, C3a and C5a receptors, did not show significant associations with allograft rejection.



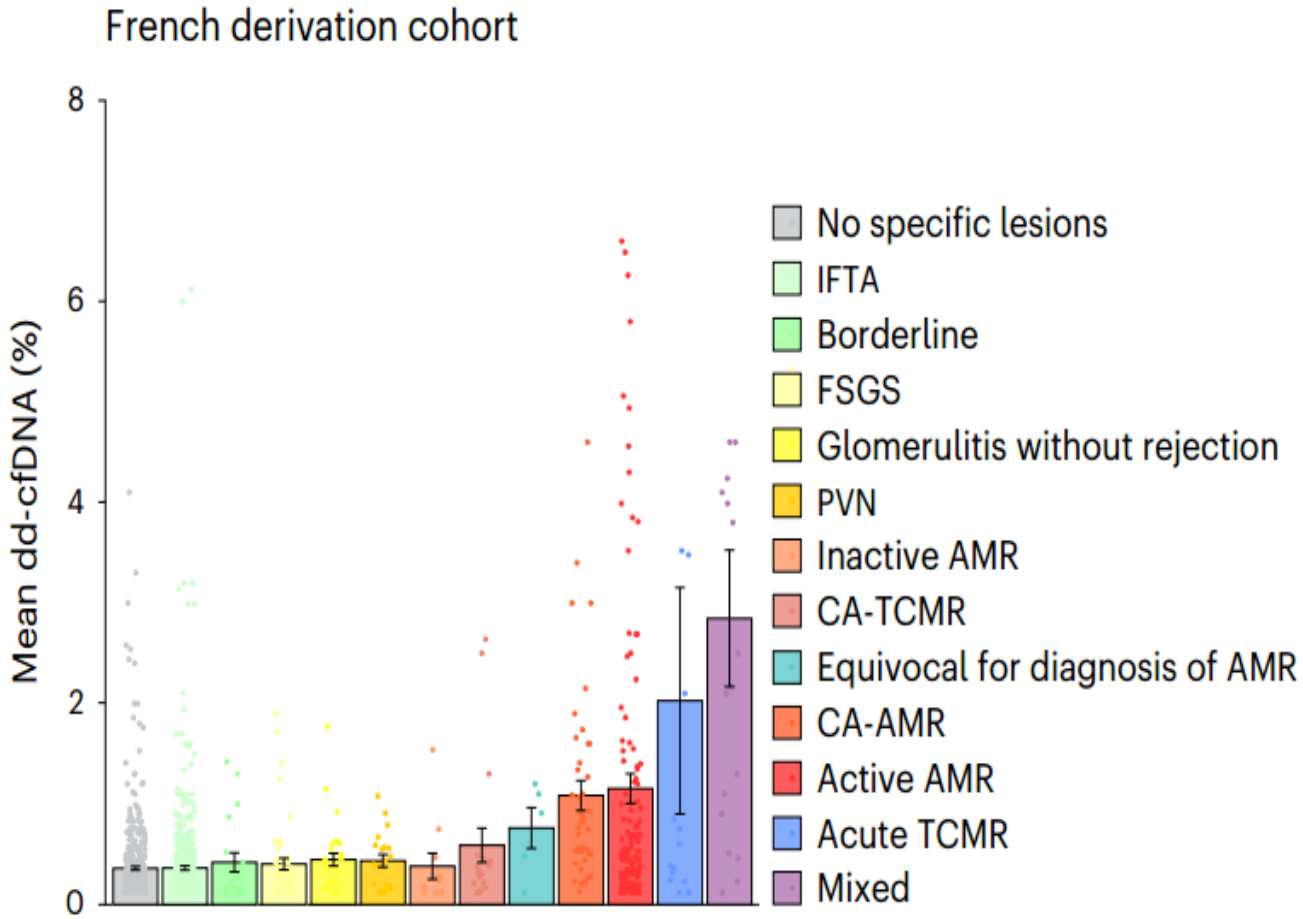
Cell-free DNA For The Detection Of Kidney Allograft Rejection

- Cell-free DNA (cfDNA) is fragmented extracellular DNA released in the bloodstream from cells undergoing apoptosis or necrosis.
- In transplantation, dd-cfDNA detected in the blood of kidney recipients has been proposed as a noninvasive biomarker to detect rejection.
- In a large multinational study, they demonstrated that elevated levels of dd-cfDNA were highly associated with the presence, activity and severity of all types of kidney allograft rejection, and showed its added value beyond standard of care monitoring in predicting rejection

Aubert et al. Nature Medicine| Volume 30 | August 2024 | 2320–2327

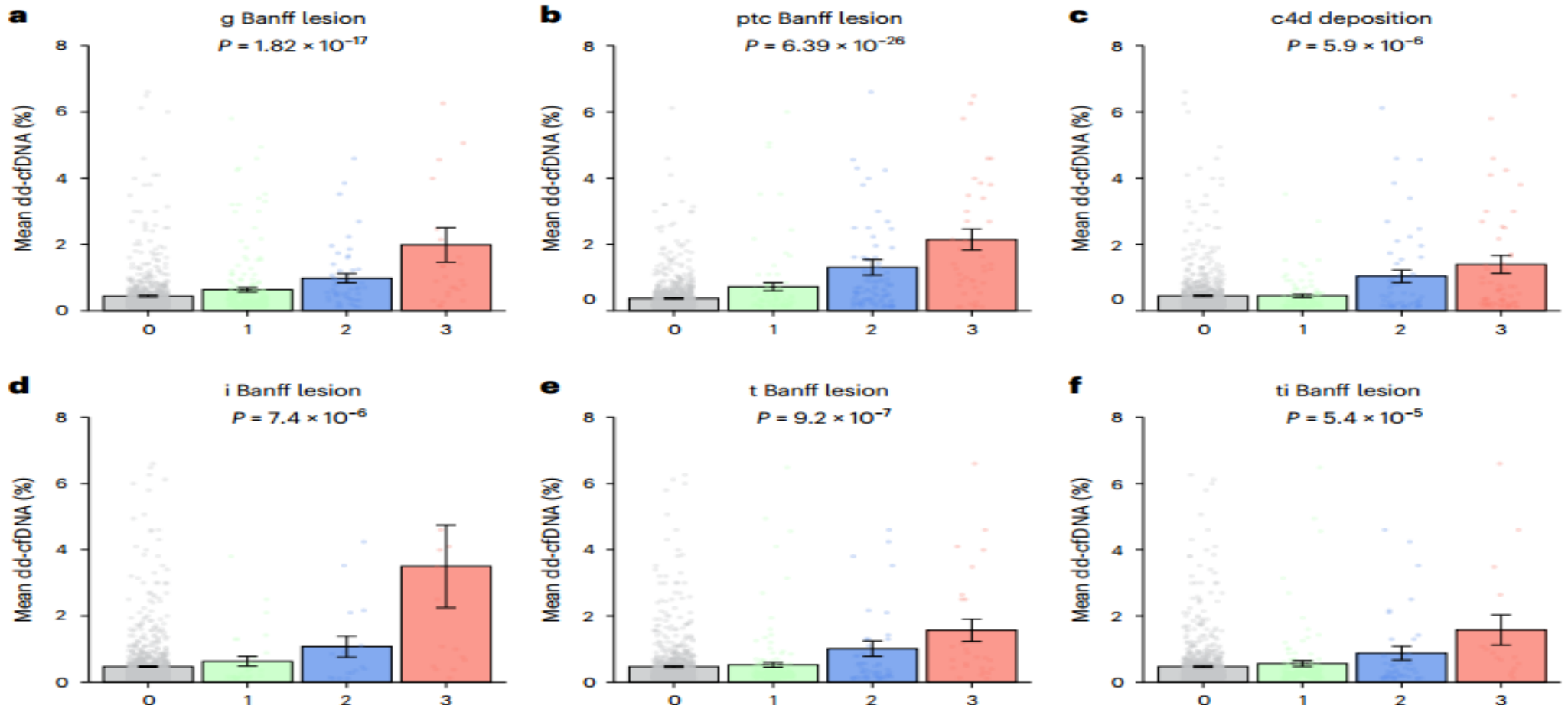
DD-cfDNA LEVELS ACCORDING TO KIDNEY ALLOGRAFT DIAGNOSES

- **2,882** kidney allograft recipients from 14 transplantation centers in Europe and the United States
- Among the 1,415 kidney allograft biopsies (38.2% for-cause biopsies and 61.8% protocol biopsies performed in clinically stable patients.
- Mean level of dd-cfDNA according to the histological biopsy results.
- Each bar corresponds to one histological diagnosis with its mean dd-cfDNA value.
- Each dot corresponds to an individual dd-cfDNA value.



The inclusion of dd-cfDNA to a standard of care prediction model showed improved discrimination (area under the curve 0.777 (95% CI 0.741–0.811) to 0.821 (95% CI 0.784–0.852); P = 0.0011) and calibration.

Association Of DD-cfDNA With Antibody-mediated Lesions And TCMR Lesions.



Chronic allograft injuries not related to rejection including arteriosclerosis, arteriolar hyalinosis, mesangial expansion and IFTA did not show elevated dd-cfDNA .

Clinical outcomes from the *A*ssessing *D*onor-derived cell-free DNA *M*onitoring *I*nsights of kidney *A*llografts with *L*ongitudinal surveillance (ADMIRAL) study.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

1094 patients

7 transplant centers

Single Kidney Adult Recipients

90% deceased donor

Multiorgan and pregnancy excluded

3 yrs. post transplant dd-cfDNA surveillance

Median of 6 results per patient

Methods

Post transplant events

Centralized biopsy reporting

Center Standard of Care protocols

3 years of Outcomes Surveillance

Analysis of
- De-Novo DSA
- eGFR trajectories
- Allograft rejection

Outcomes

eGFR Decline

Persistently elevated dd-cfDNA (>1 result above 0.5%) predicted a > 25% decline in eGFR over 3 years

Temporal Relationship

dd-cfDNA values ≥ 0.5% were associated with a nearly 3-fold increase in the risk of development of de novo donor specific antibody (DSA)

Subclinical Rejection

Significant elevations in dd-cfDNA during rejection ahead of changes in serum creatinine

Bu et al 2021

ClinicalTrials.gov Identifier: NCT04566055

CONCLUSION: *The ADMIRAL study demonstrates a broad utility of dd-cfDNA as a leading indicator ahead of clinical presentations of allograft injury, formation of dnDSA, eGFR decline and subclinical rejection.*

Acute Kidney Injury In The Donor DGF And Risk Of Graft Failure

Current evidence :

Standard-risk donors, donor AKI does not impair transplantation outcomes.

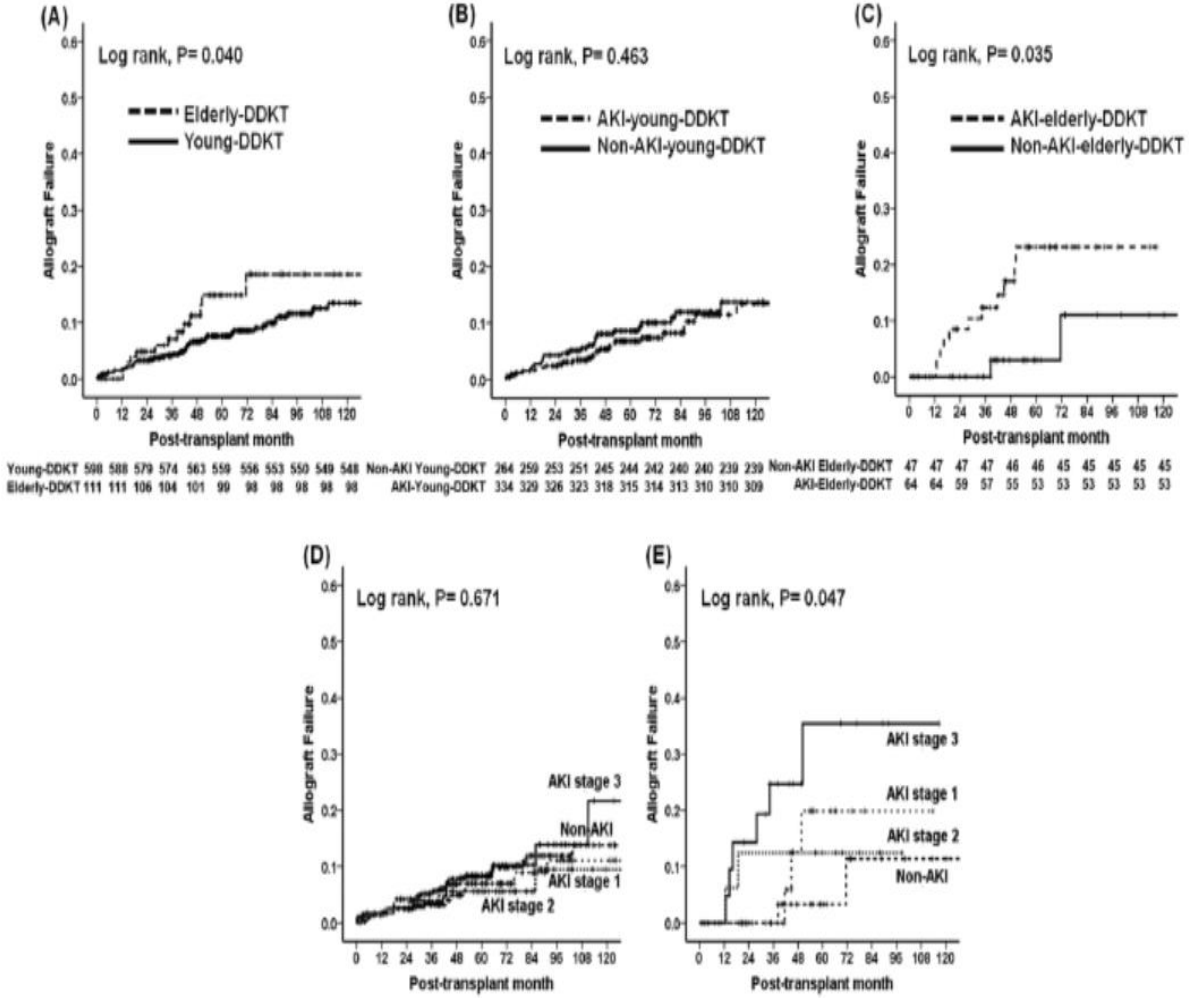
The evidence is less convincing for marginal donors, such as elderly donors or donors with elevated KDPI (e.g., above 85%).

Suggestion:

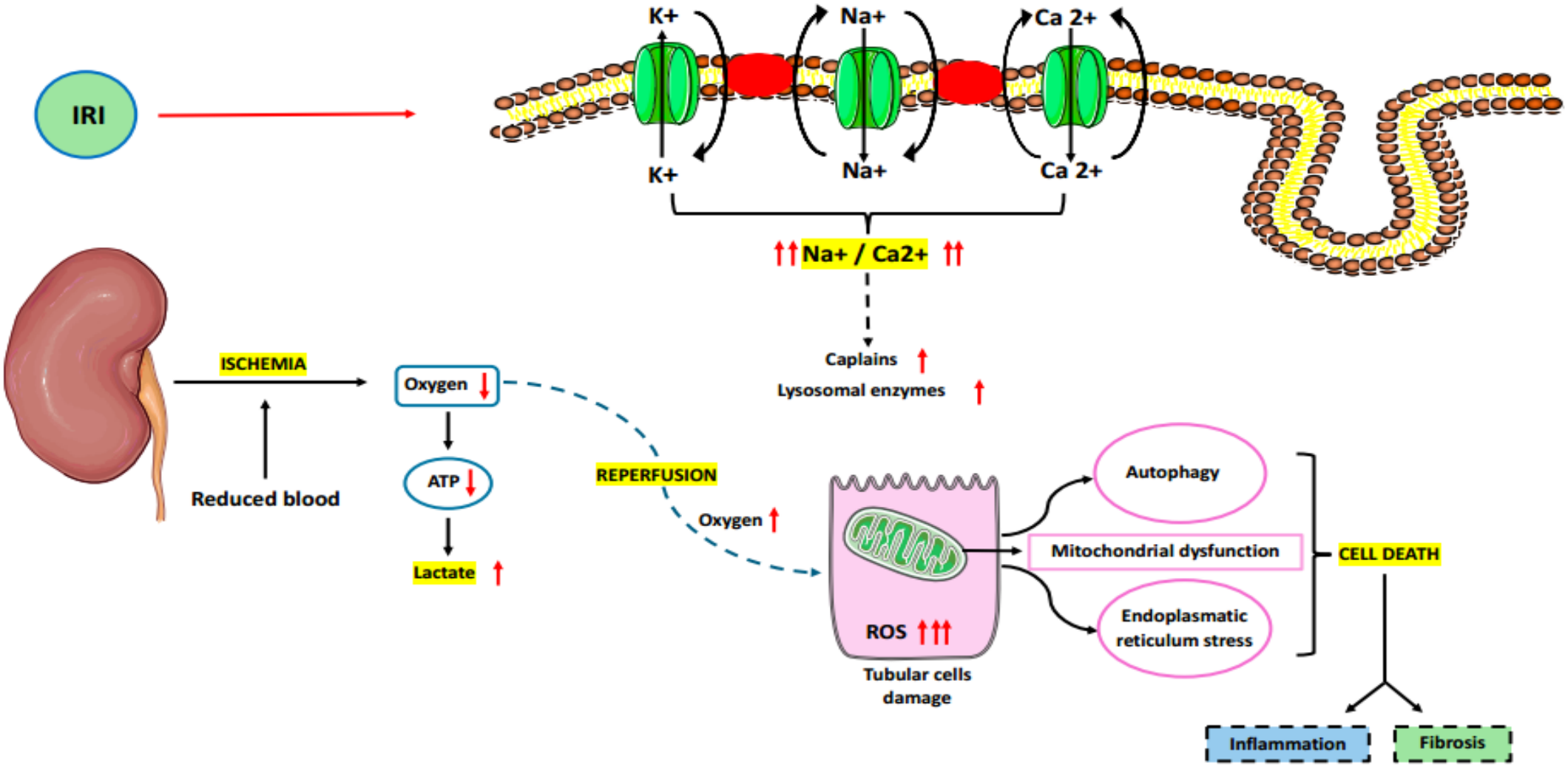
Protocols for organ quality assessment

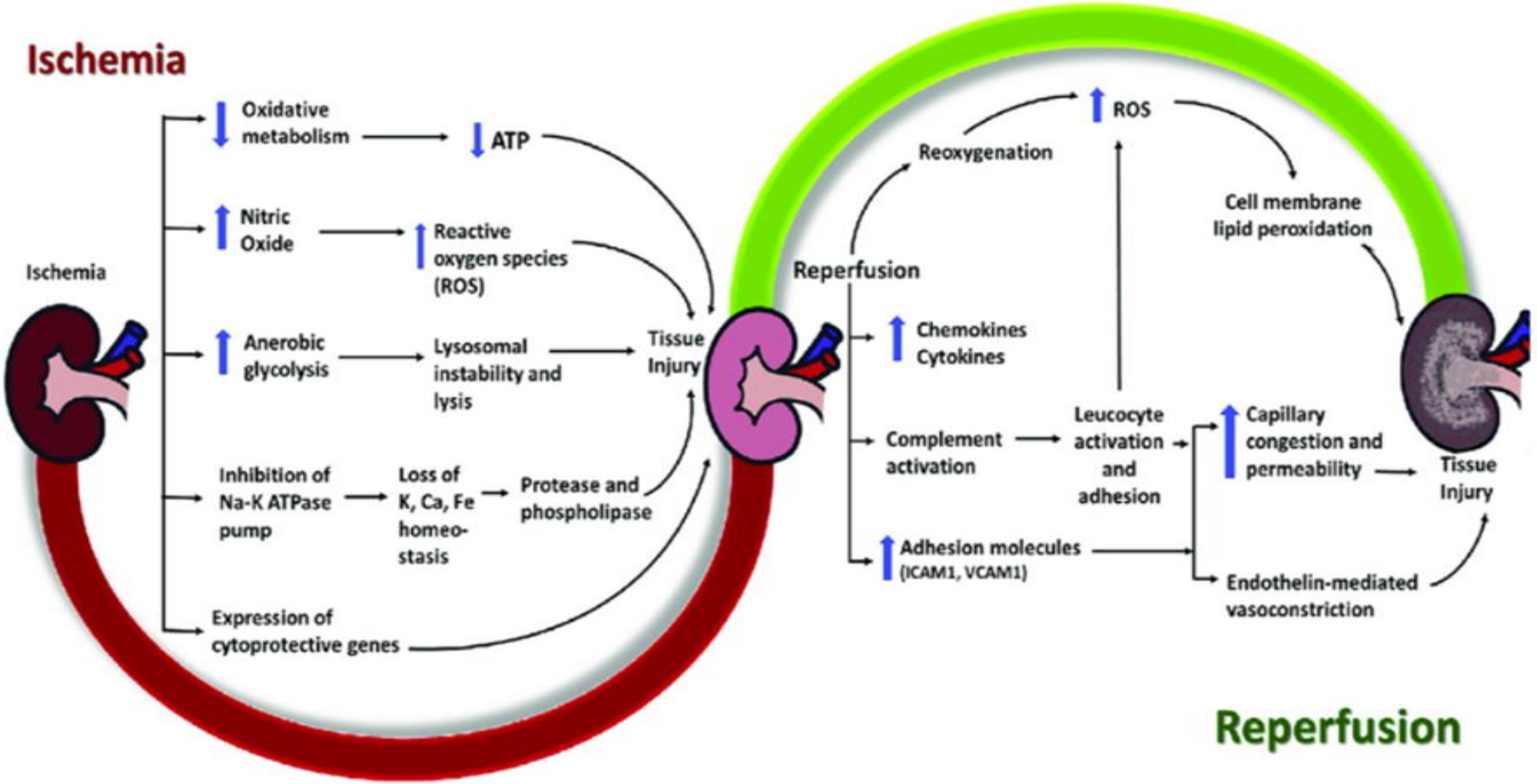
Minimization of cold ischemia times

Use of machine perfusion

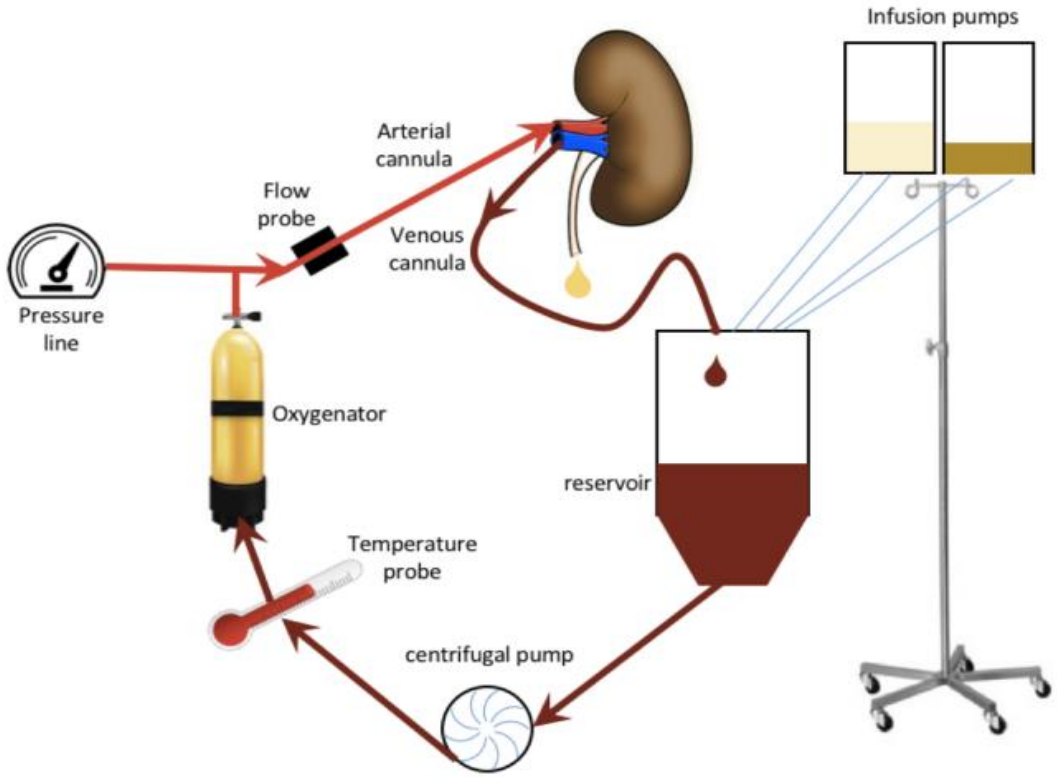


PATHOPHYSIOLOGY OF ISCHEMIA–REPERFUSION INJURY




Ischemia
Oxidative metabolism
ATP
Nitric Oxide
Reactive oxygen species (ROS)
Anerobic glycolysis
Lysosomal instability and lysis
Tissue Injury
Inhibition of Na-K ATPase pump
Loss of K, Ca, Fe homeo-stasis
Protease and phospholipase
Expression of cytoprotective genes
Ischemia
Reperfusion
ROS
Reoxygenation
Cell membrane lipid peroxidation
Chemokines Cytokines
Complement activation
Leucocyte activation and adhesion
Capillary congestion and permeability
Tissue Injury
Adhesion molecules (ICAM1, VCAM1)
Endothelin-mediated vasoconstriction
Reperfusion

SCHEMATIC DIAGRAM OF KIDNEY NORMOTHERMIC MACHINE PERFUSION SYSTEM



- Arrows indicate direction of blood flow.
- The renal artery and vein are cannulated.
- Urine is collected for measurement and analysis.
- Real-time recording of renal physiology and samples of blood perfusate and urine can be sampled to monitor reconditioning.

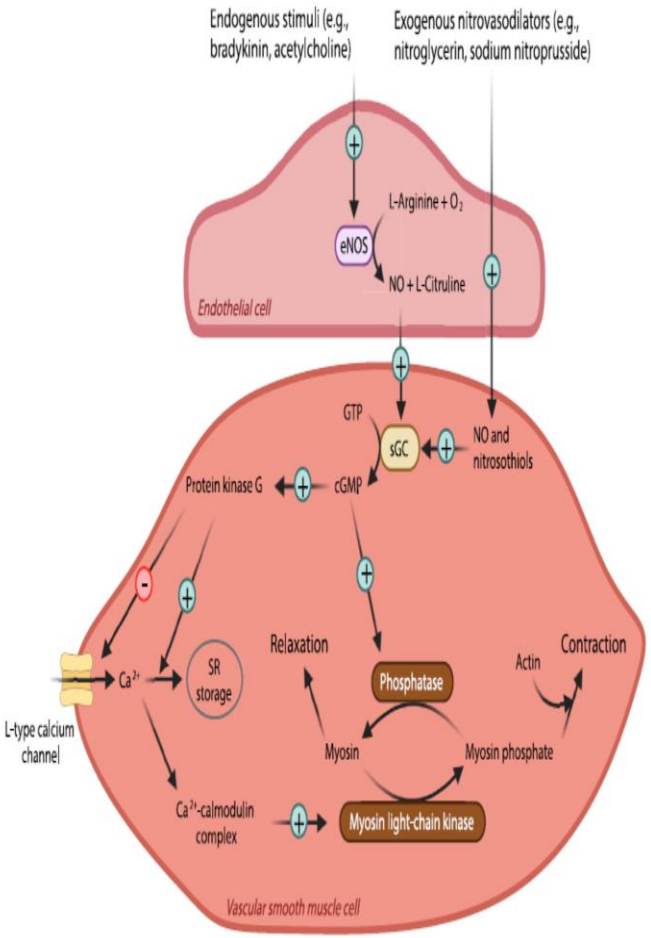
Hypothermia or Machine Perfusion in Kidney Donors

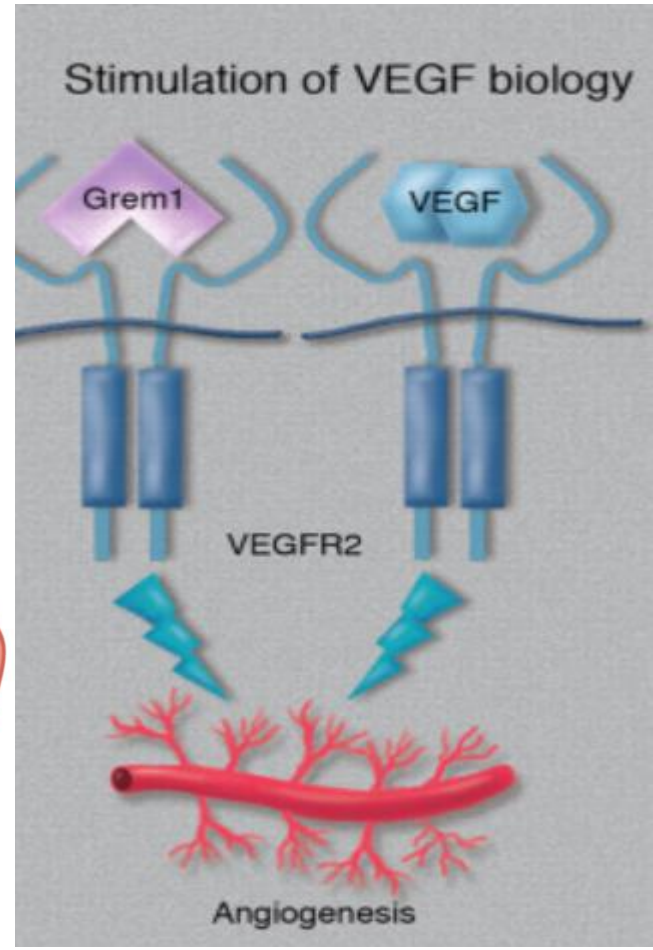
Darren Malinoski, M.D., Christina Saunders, Ph.D., Sharon Swain, M.S.N., R.N., Tahnee Groat, M.P.H., Patrick R. Wood, M.D., Jeffrey Reese, M.D., Rachel Nelson, M.S., Jennifer Prinz, M.P.H.-H.P.A., B.S.N., Kate Kishish, R.N., Craig Van De Walker, M.S., P.J. Geraghty, M.B.A., Kristine Broglio, M.S., and Claus U. Niemann, M.D.

- DGF was reported to be 38% lower with the use of therapeutic hypothermia (34 - 35°C) than the use of normothermia in brain dead organ donors.
- Machine perfusion of kidneys obtained from brain-dead donors is performed in approximately **32% - 38%** of all kidneys considered for Tx in the US.
- **Hypothesis**: Mild hypothermia was non-inferior to machine perfusion and cost savings.
- A pragmatic, adaptive, prospective, randomized trial to assess targeted mild hypothermia vs. effective machine perfusion of kidneys from brain-dead donors.

Perfusate/Blood Flow To The Kidney

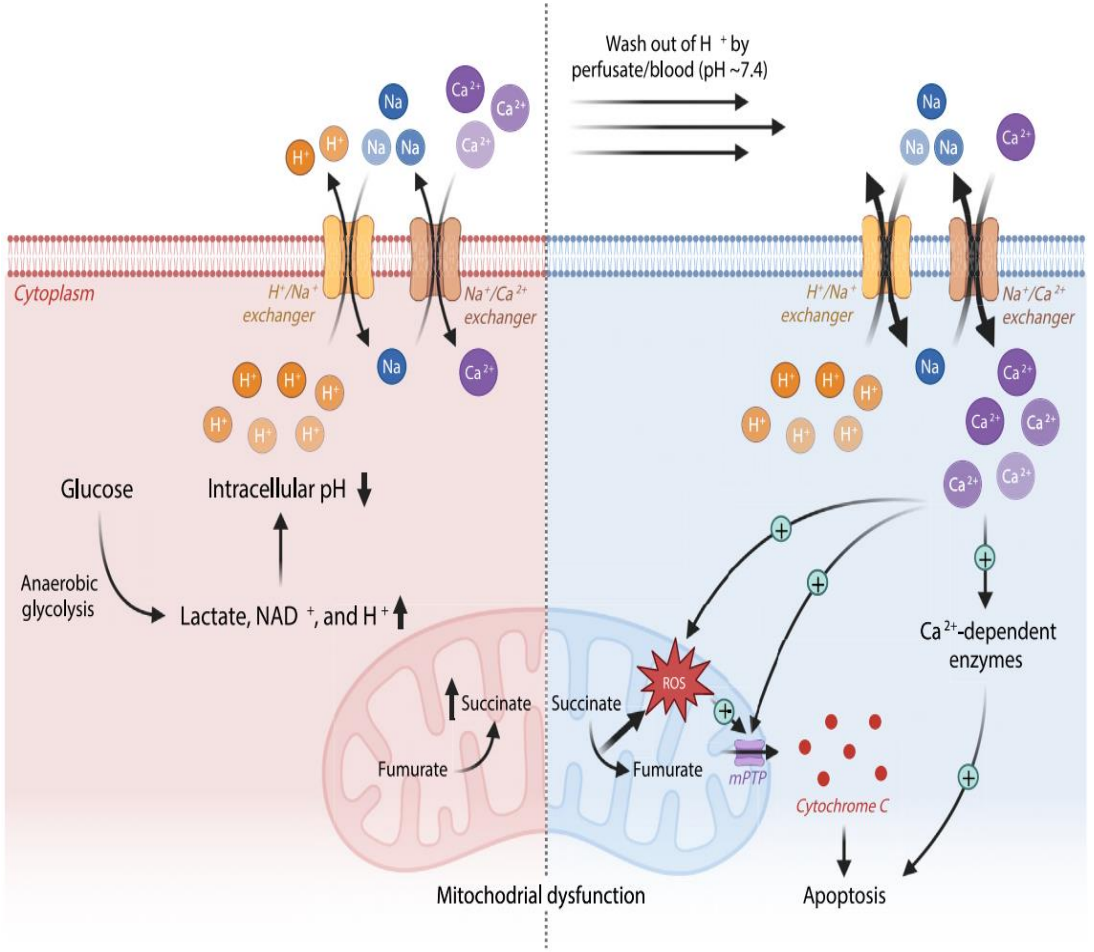
- Use of calcium channel blockers (such as verapamil or diltiazem). A low calcium concentration prevents the activation of calcium-dependent proteases, phospholipases, and endonucleases.
- NO-precursors (nitrates such as nitroglycerin)
- Addition of VEGF agonists and agents that inhibit angiogenesis inhibitors.

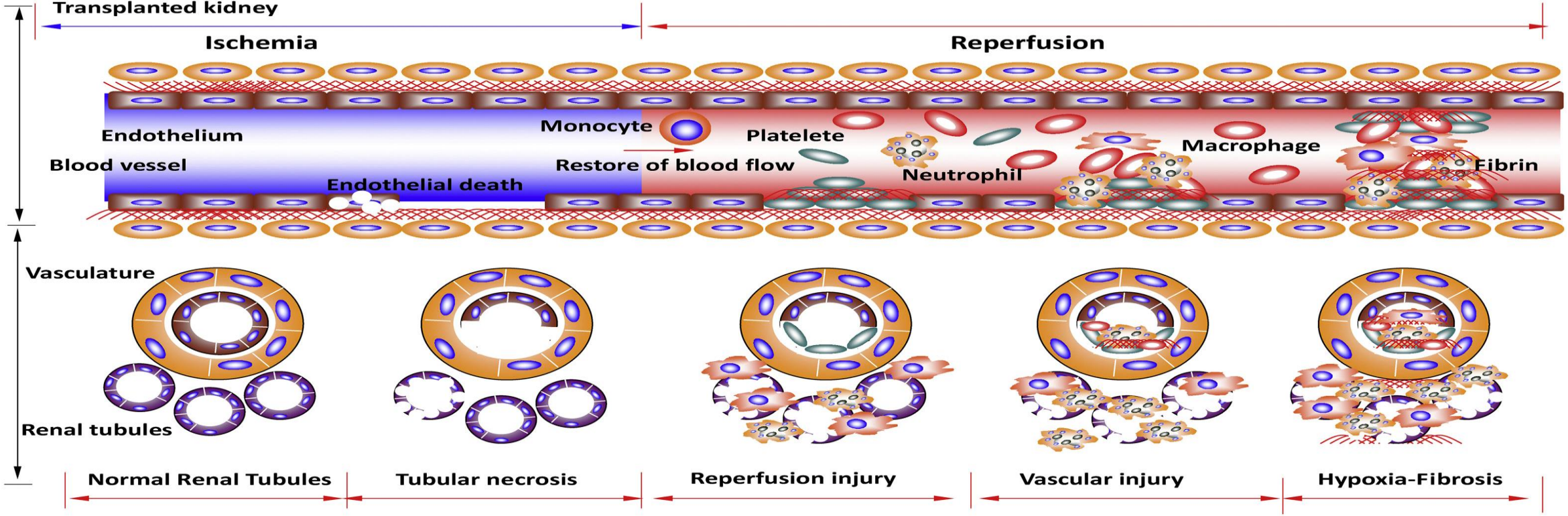




Oxidative Damage& defective NAD Biosynthesis/ Increased NAD Consumption

- Exogenous antioxidants (such as vitamins C and E, carotenoids, flavonoids, and isoflavones) and mitochondrial-targeted antioxidants (such as MitoQ) can counteract oxidative damage
- Pyruvate has antioxidant and anti-inflammatory properties, thereby potentially mitigating oxidative damage
- Supplementation of NAD -precursors such as nicotinamide, nicotinamide mononucleotide, or vitamin B3, Fatty acid, pyruvate and citrate

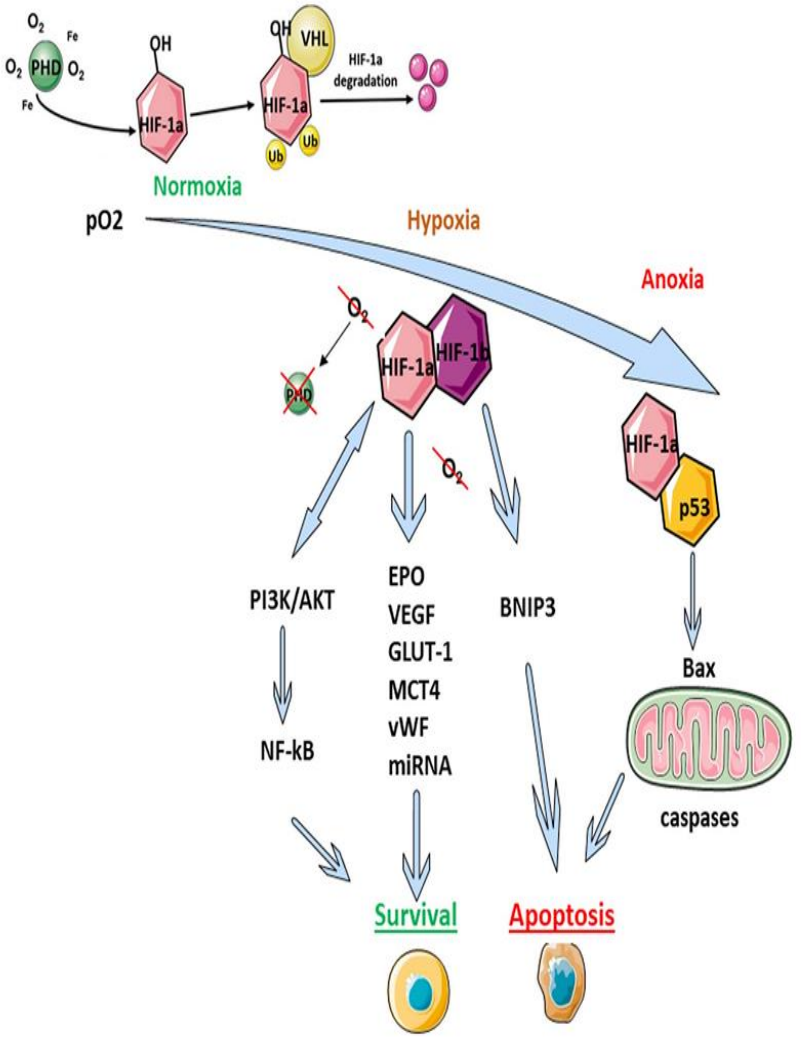




Renal edema and microthrombi: Administration of tissue plasminogen activator and plasminogen to the perfusate at the initiation of NMP effectively eradicates microvascular obstructions
Capillary rarefaction Addition of VEGF agonists and agents that inhibit angiogenesis inhibitors. However, such interventions would presumably be more effective with prolonged NMP

Work Load And Signaling Pathways

- Furosemide can attenuate renal injury by increasing oxygen availability in the outer medulla
- SGLT2 inhibitors can reduce progression of renal injury and disease by altering renal metabolism. **Luseogliflozin**, an SGLT2 inhibitor, attenuates fibrosis and microvascular injury, and augments VEGF expression in the kidneys after IRI
- Inhibiting PHD enzymes (for example with **Enarodustat** and **Daprodustat**) to enhance HIF signaling and stimulate erythropoiesis, anaerobic glycolysis, and angiogenesis

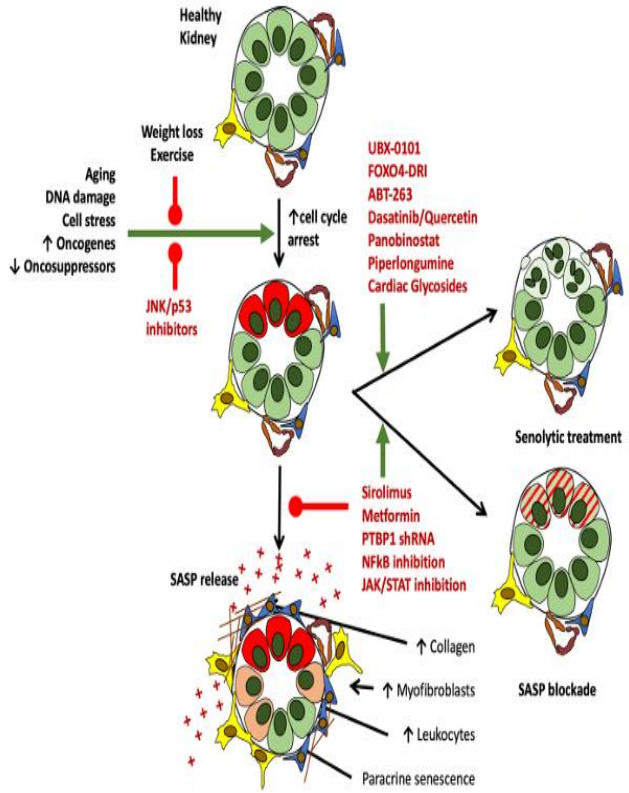


Senolytics

Senolytics, a class of drugs designed to specifically target senescent cells—those that have ceased cell division

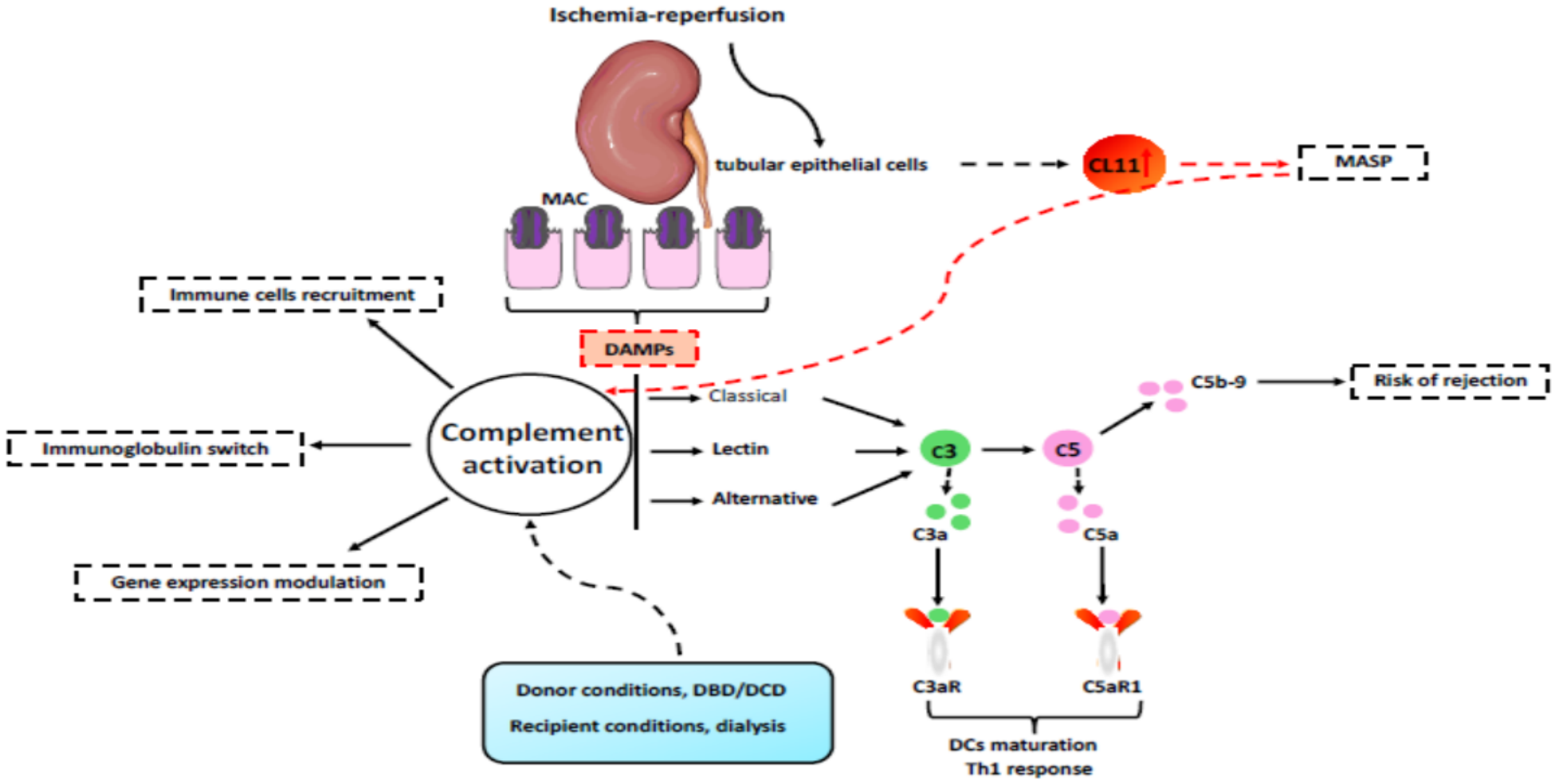
A combination of the senolytics **Dasatinib and Quercetin** was administered prior to IRI in mice, it resulted in decreased levels of cell-free mitochondrial DNA while alleviating systemic inflammation and prolonging organ survival in older mice.

It is expected that senolytics can play a prominent role in rejuvenating allografts from older deceased donors during NMP.



Docherti et al. J Am Soc Nephrol. 2019;30(5):726–

Complement System Activation During Ischemia Reperfusion Injury



Lasorsa et al. Int. J. Mol. Sci. 2024, 25,

What are the 3-year outcomes of an RCT assessing the safety and efficacy of C1 esterase inhibitor for prevention of DGF?

CJASN
Clinical Journal of American Society of Nephrology

Methods and Cohort

Post-hoc analysis of a phase I/II RCT

70 recipients of deceased donor kidney transplants at risk for DGF

C1 esterase inhibitor 50 U/kg
N=35

Placebo
N=35

Follow-up of 3.5 years

Outcomes

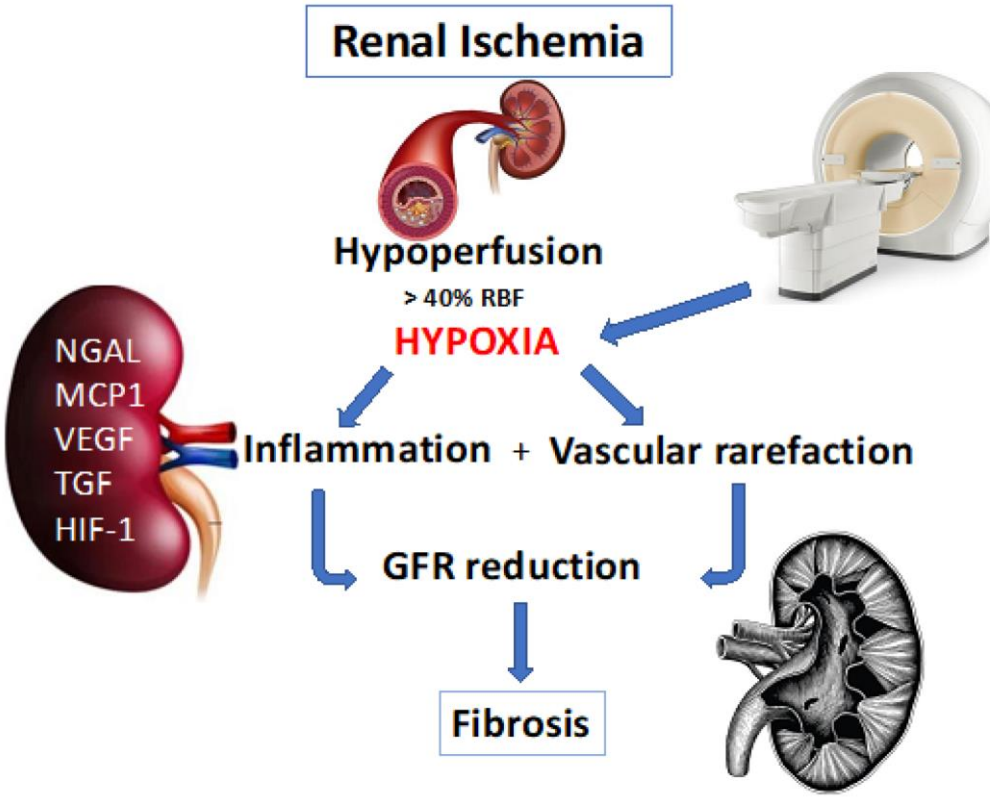
eGFR slope ml/min/1.73m²/year	eGFR at 3.5y ml/min/1.73m²	Cumulative incidence of graft failures	Deaths
0.5 (-4, 5)	56 (42, 70)	3%	3
-4 (-8, -0.1)	35 (21, 48)	21%	0

Conclusion Treatment of patients at risk for ischemia-reperfusion injury and delayed graft function with C1 esterase inhibitor was associated with lower incidence of graft failure.

Edmund Huang, Ashley Yo, Jua Choi, et al. ***Three-Year Outcomes of a Randomized, Double-Blind, Placebo-Controlled Study Assessing Safety and Efficacy of C1 Esterase Inhibitor for Prevention of Delayed Graft Function in Deceased Donor Kidney Transplant Recipients.*** CJASN doi: 10.2215/CJN.04840419. **Visual Abstract by Beatrice Concepcion, MD**

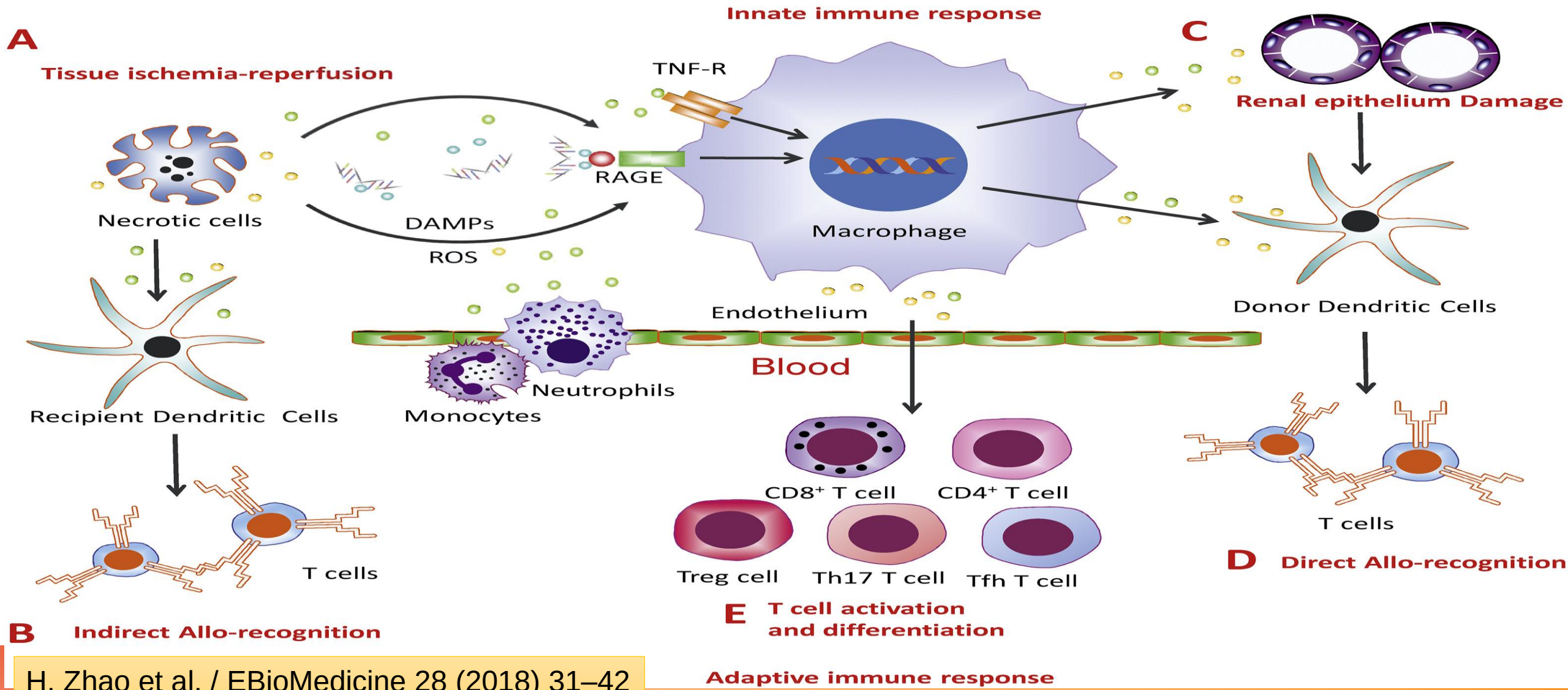
Fibrosis

- Excessive preexisting fibrosis IRI-induced damage and a chronic allogenic immune response, induce an excess deposition of ECM.
- Van Leeuwen et al were the first to explore the impact of **Galunisertib** (TGF beta inhibitor) during 6 hours of NMP, revealing a reduction in IL-6 and transforming growth factor-β1 levels in treated kidneys.



Br J Pharmacol. 2023. https://doi.org/10.1111/bph.16220.

Ischemia-reperfusion Injury And Allo-immune Response



H. Zhao et al. / EBioMedicine 28 (2018) 31–42

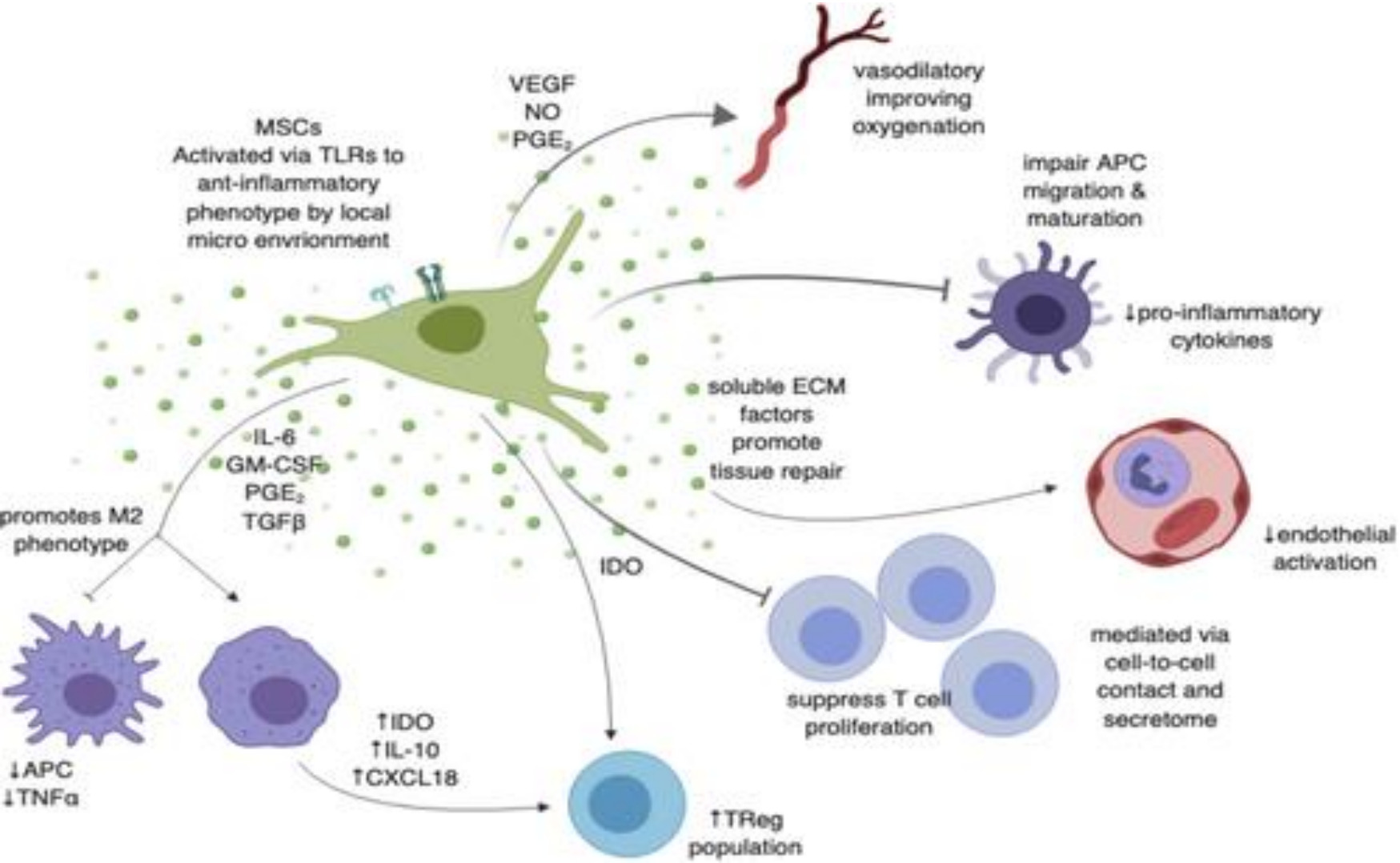


Table 1. Summary of ISCT criteria to identify mesenchymal stromal cell.

(1) Adherence–they must be plastic adherent in standard culture conditions		
(2) Phenotype	Positive (>95%+)	Negative (<2%+)
	CD105	CD45
	CD73	CD34
	CD90	CD14 or CD11b
		CD79alpha or CD19
		HLA-DR
(3) In vitro differentiation potential: osteoblasts, adipocytes, chondroblasts under standard in vitro differentiating conditions		

Mesenchymal stromal cells are a population of adult, adherent, multipotent, stromal cells of mesodermal origin. Multipotent adult progenitor cells and MSCs have both demonstrated in numerous studies a profound ability to reduce ischaemia reperfusion injury and the inflammatory response associated with solid organ transplantation .

Thompson et al. Transplant International 2021; 34: 49–

CELL THERAPY

- Two cell therapies have garnered the most attention :**Mesenchymal stromal cells** (**MSCs**) and **Multipotent adult progenitor cells** (**MAPCs**).

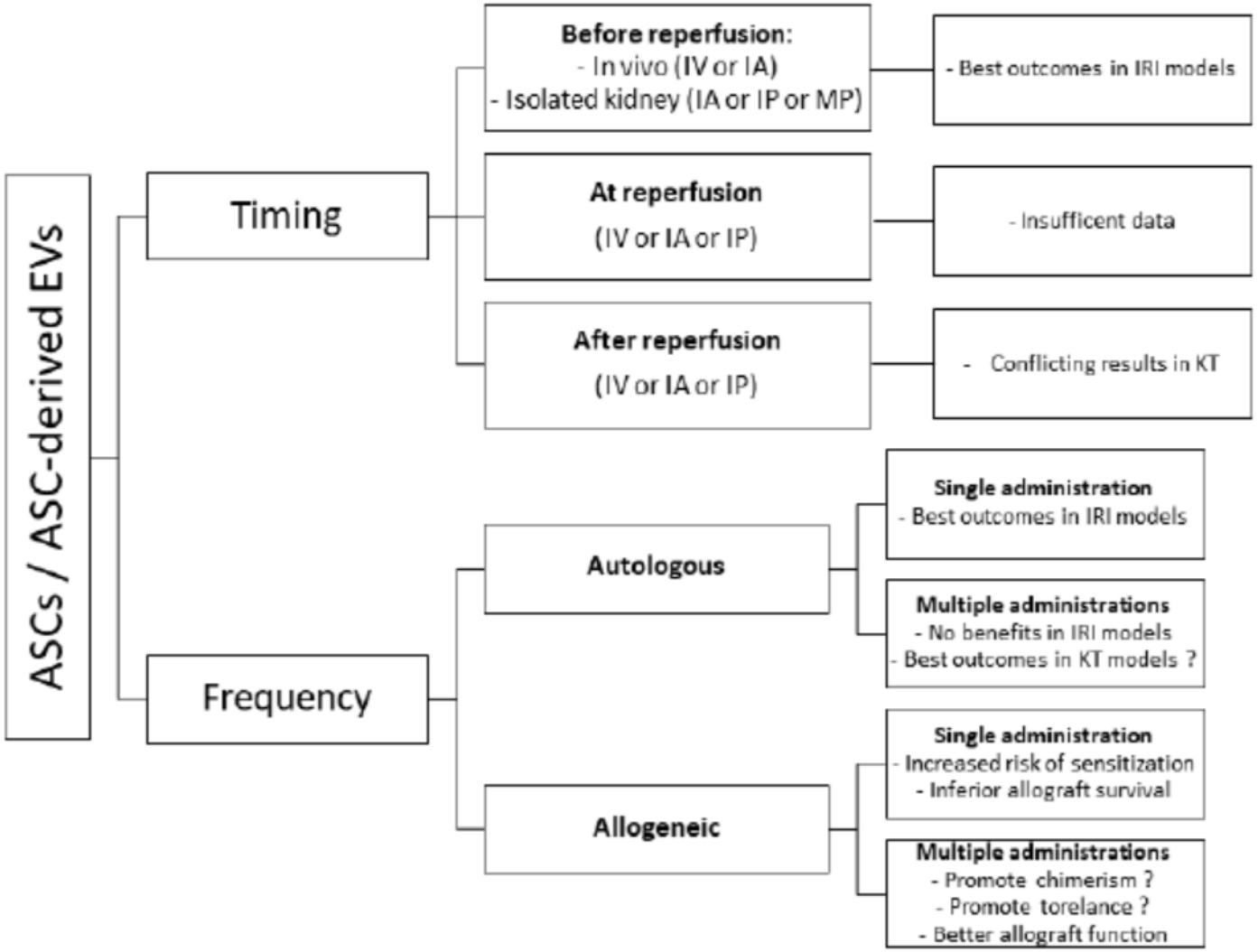
Sources

Fetal

- Wharton's jelly
- Umbilical Cord blood
- Placenta
- Amniotic Fluid
- Chorionic Villi

Adult

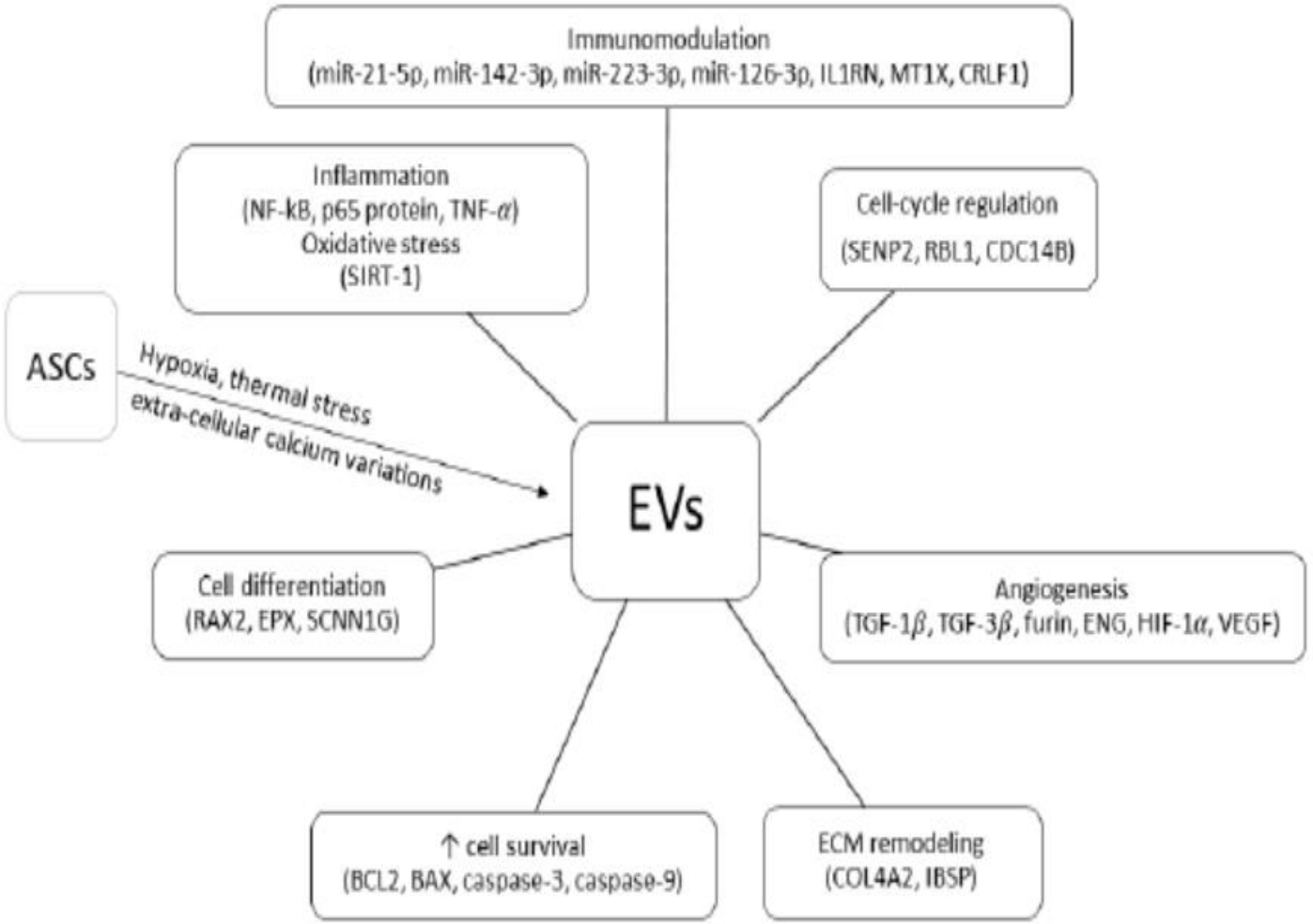
- Bone Marrow
- Adipose Tissue
- Dental Pulp
- Blood
- Yellow Ligament
- Endometrium
- Mother's Milk



Deo et al. Pharmaceutics 2022, 14,

Extracellular Vesicles (Evs)

- EVs are nano-sized particles with the capability to target damaged cells and convey the biological effects of their parent stem cells.
- **Gregorini et al** showed EV-treated kidneys exhibited reduced oxidative damage, significantly lower levels of inflammatory markers, and decreased lactate dehydrogenase levels in the perfusate



Predictors and Adverse Outcomes of Acute Kidney Injury in Hospitalized Renal Transplant Recipients

292 Renal Transplant Recipients (RTRs)

807 Hospital Admissions

Acute Kidney Injury (AKI) = difference of ≥50% between peak Scr during admission and baseline Scr in **149/292** RTRs **(51%)**

Risk factors for in-hospital AKI

Infection (OR 2.93)

AKI in a previous admission (OR 2.13)

Medical history of Hypertension (OR 1.91)

Low SBP during admission (OR 0.98)

High CNI level (OR 1.08)

Low Hemoglobin (OR 0.9)

Low Albumin (OR 0.51)

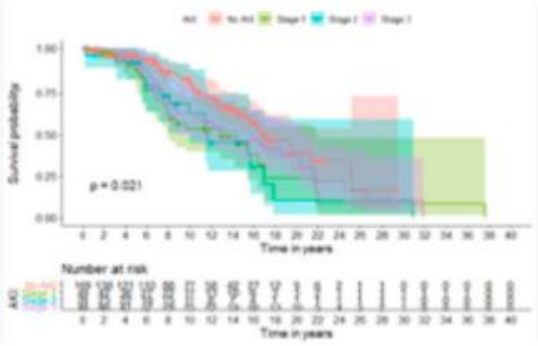
Outcomes of in-hospital AKI

Length of stay ↑ (3.83 vs. 7.01 days)

In-hospital Mortality ↑ (1.6% vs. 10.8%)

Re-hospitalization within 90 days from discharge ↑ (OR 1.95)

Overall mortality ↑



In-hospital AKI is common in RTRs and is associated with poor short- and long-term outcomes.

TAMMY HOD et al. *Transpl. Int.* 2023
doi: 10.3389/ti.2023.11141

ESOT Leading the way in transplantation

Transplant International

GRAPHICAL ABSTRACT |

Predicting Long-term Outcomes Of Kidney Transplantation In The Era Of Artificial Intelligence

- **Artifcial intelligence**: AI is a branch of computer science that involves the use of computers to model intelligent behavior with minimal human intervention. AI is widely used in medicine to analyze complex medical data in the diagnosis, treatment, and prediction of outcomes.
- 407 KTs (living + deceased donors) model and prediction of 5 year graft survival
- History of hypertension, history of transfusion, duration on dialysis before KT, donor age, AKI post-KT, Acute rejection, CMV infection, length of the 1st hospitalization, 3-month eGFR, MMF therapy were factors in their model.
- AUC: 89.7% , Sensitivity: 91%, Specificity: 87%

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