Untargeted NMR-based analysis of kidney allograft perfusates identifies a metabolomic signature of delayed graft function

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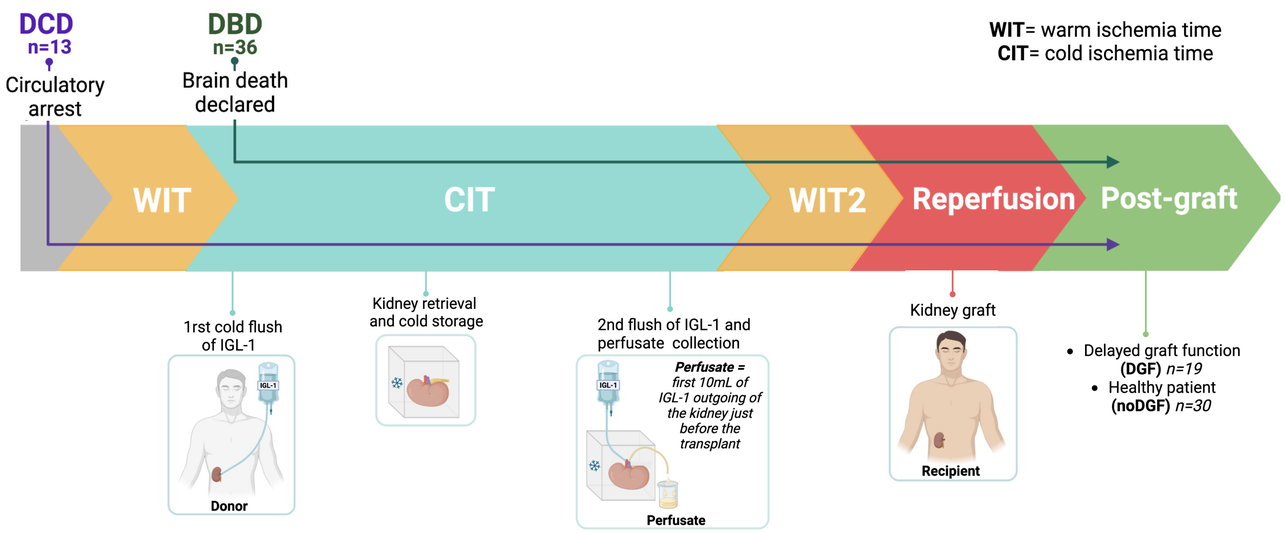
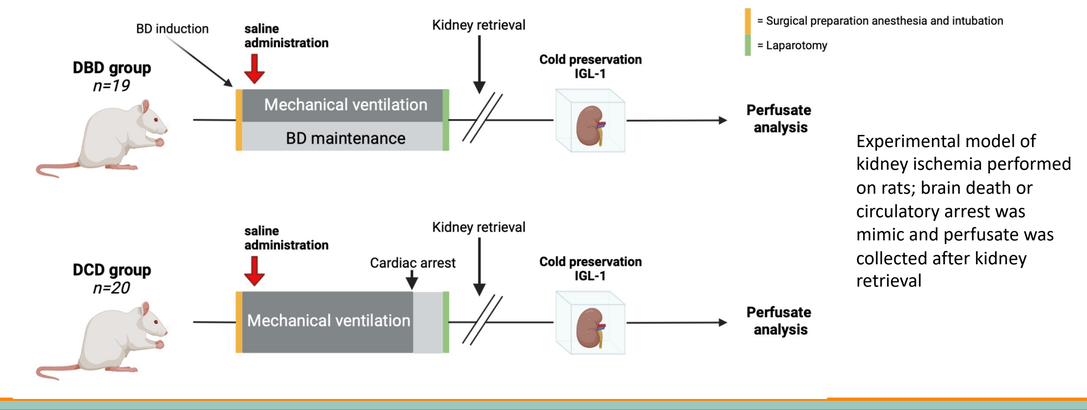
MATERIALS AND METHODS

Human study



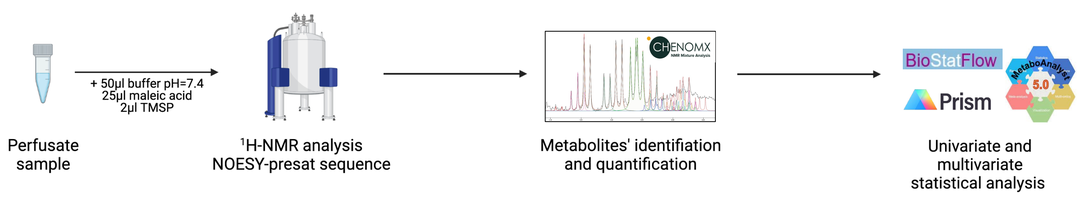
Timeline of kidney transplantation starting from the death of donor (DBD/DCD) until post-graft recovery (DGF/noDGF).
Perfusate collection take place during cold ischemia time.

Experimental model



Experimental model of kidney ischemia performed on rats; brain death or circulatory arrest was mimic and perfusate was collected after kidney retrieval

^{1}H-NMR metabolomics



INTRODUCTION

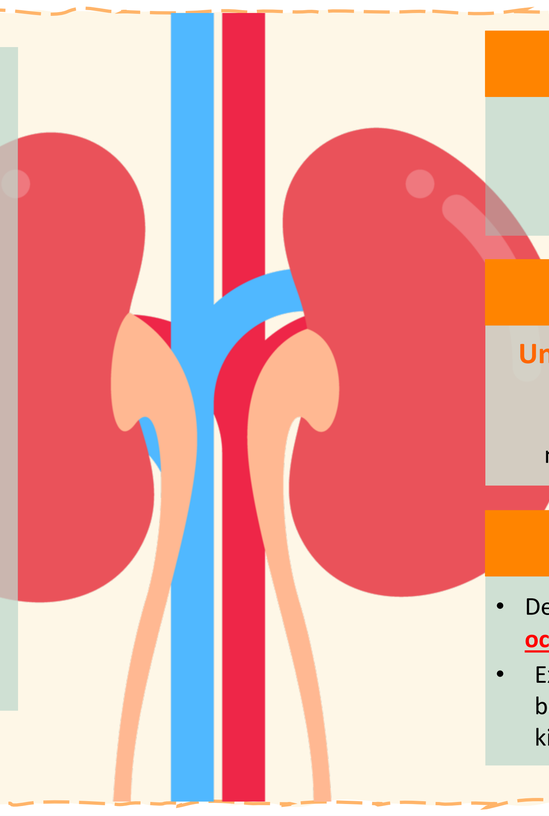
Kidney transplantation (Ktx) represent the **best treatment** for patient with end stage renal disease

90.000 Ktx are performed each year worldwide, but the outcome still depends on graft quality

The increasing gap between demand and supply for Ktx has **expanded the donor criteria** by adding to dead brain donor (DBD) the dead circulatory donor (DCD)

Kidneys from suboptimal donors are exposed to prolonged ischemic event and poorer graft outcomes and higher risk to undergo **delayed graft function (DGF)** in post-transplantation period

Use of a cold storage solution (IGL-1) to be flushed in the organ demonstrated to reduce DGF incidence and to **minimize ischemic damage**



Need

Reliable tools are need for assess the graft quality *after* procurement and storage ***before*** its transplantation

Solution

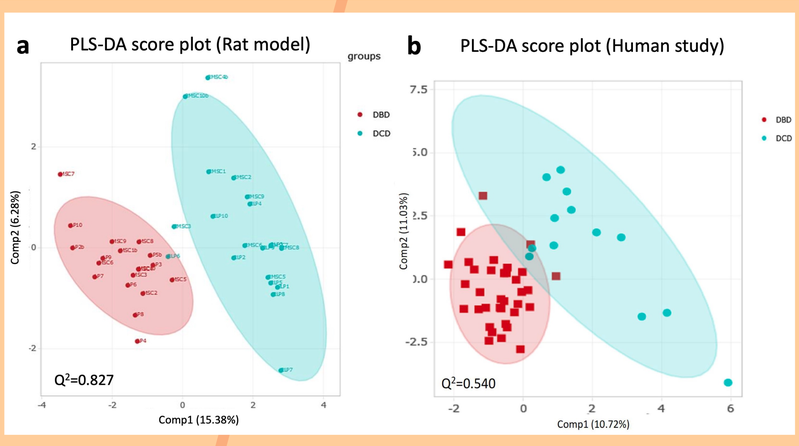
Untargeted NMR- based metabolomics approach is a noninvasive method allowing an all-in-one detection of metabolites related to pathological status

Objectives

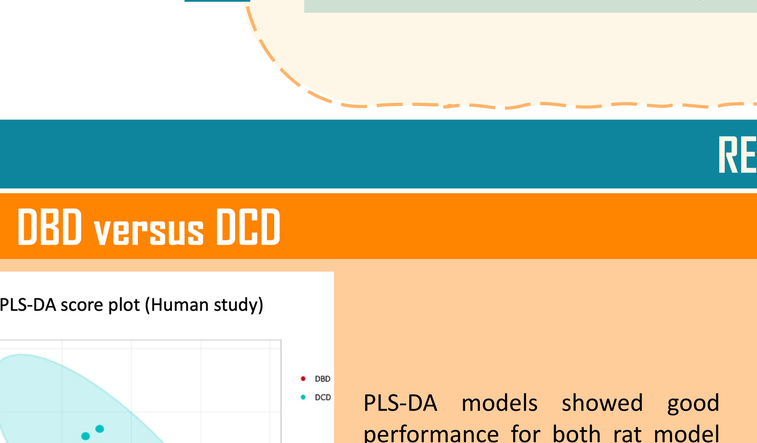
- Define a panel of **biomarkers predicting** the **occurrence of DGF** post transplantation
- Explore **the biochemical events** occurring between death and hypothermic storage of kidney

RESULTS

DBD versus DCD



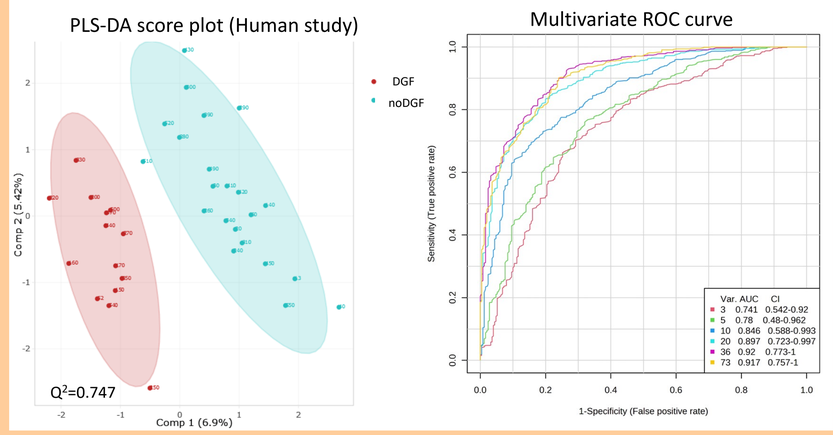
PLS-DA models showed good performance for both rat model and human study (Q^2=0.827; Q^2=0.540 respectively) and were validated through significant permutation tests.

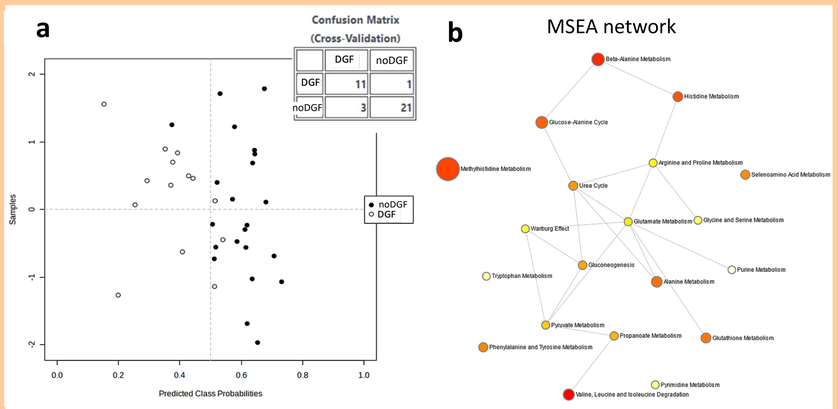


MSEA analysis led to the identification of several common pathways significantly affected by donor type able to better explore the biochemical events occurring between the death and the hypothermic storage of kidney.

DGF versus noDGF

A poor performance for distinguish all samples based on DGF kidney outcome was obtained (data not showed).
However, PLS-DA model on DBD perfusate was generated (Q^2=0.747); furthermore, the multivariate ROC curve showed a good performance (73 variables; AUC= 0.917; pred.accuracy= 83%).





A confusion matrix was additionally performed in way to cross-validate the model. To identify biologically meaningful patterns a MSEA analysis was done showing that methylhistine/ beta-alanine metabolism and valine, leucine and isoleucine degradation are the pathways more significantly impacted.

CONCLUSION AND PERSPECTIVE

Our analysis on experimental and clinical model allowed us to identify a subset of metabolites that distinguished DCD and DBD graft at metabolic level in both animal and human. The biochemical pathways implicated in donor type separation were already described in the literature in the context of liver transplantation1. Concerning analysis based on prediction of DGF kidney outcome, the higher levels of metabolites in noDGF condition are related to sustained metabolic activity as observed by Guy et al2. ; in contrast, higher levels of metabolites in DGF kidneys are linked to the higher ischemical damage of kidney 3,4,5. By considering all the obtained results and their limitations, we suggest the analysis of a new cohort in way to confirm the metabolic profile of donor type and DGF kidneys, and to evaluate the putative biochemical pathways involved. Based on the literature and in the light of our result, we believe that NMR-based metabolomics approach applied to perfusate may represents a robust tool to monitor quality graft in pre-transplantation event and guide clinicians in management of DGF graft.

References

[1]Hrydziuszko et al., 'Mass Spectrometry Based Metabolomics Comparison of Liver Grafts from Donors after Circulatory Death (DCD) and Donors after Brain Death (DBD) Used in Human Orthotopic Liver Transplantation'.
[2]Guy et al., 'Metabolomic Analysis of Perfusate During Hypothermic Machine Perfusion of Human Cadaveric Kidneys'
[3]Kurata et al., 'Renoprotective Effects of l -Carnosine on Ischemia/Reperfusion-Induced Renal Injury in Rats'.
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