

Optimisation of DCD donor livers – Removal of extracellular histones during NMP and following whole blood reperfusion in an ex-situ porcine model

Syed Hussain Abbas^{1*} & Fungai Dengu^{1*}, Jeremy Schofield², Guozheng Wang², Alireza Morovat³, Alberto Quaglia⁴, Simon T Abrams², Cheng-Hock Toh², **Andrew Aswani^{5,6**} & Peter Friend^{1**}**

***Joint first authors & **Joint senior authors**

Nuffield Department of Surgical Sciences, University of Oxford¹

Department of Clinical Infection, Microbiology and Immunology, University of Liverpool, Liverpool²

Department of Clinical Biochemistry, Oxford University Hospitals NHS Foundation Trust³

Department of Histopathology, University College London⁴

Santarus AG, Zurich⁵

Guy's & St Thomas's NHS Foundation Trust⁶

Hypothesis & Aims

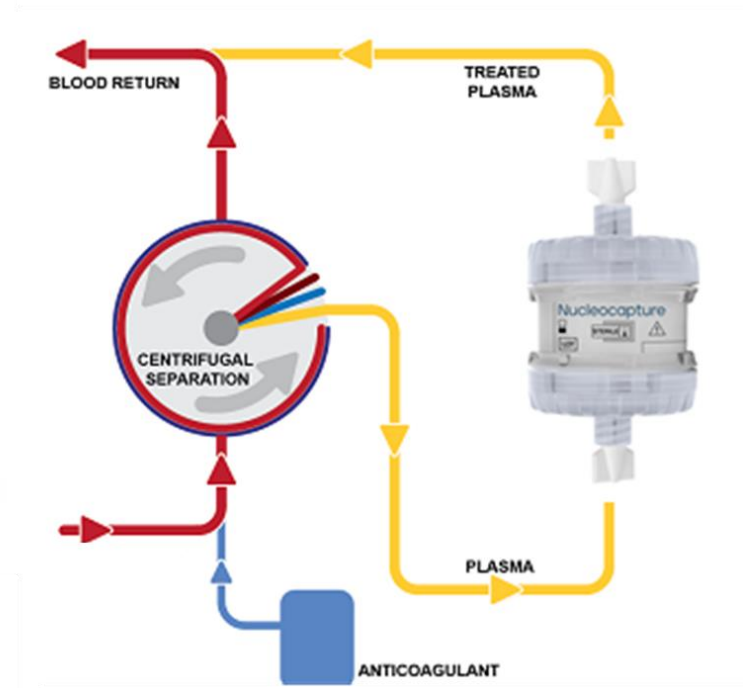
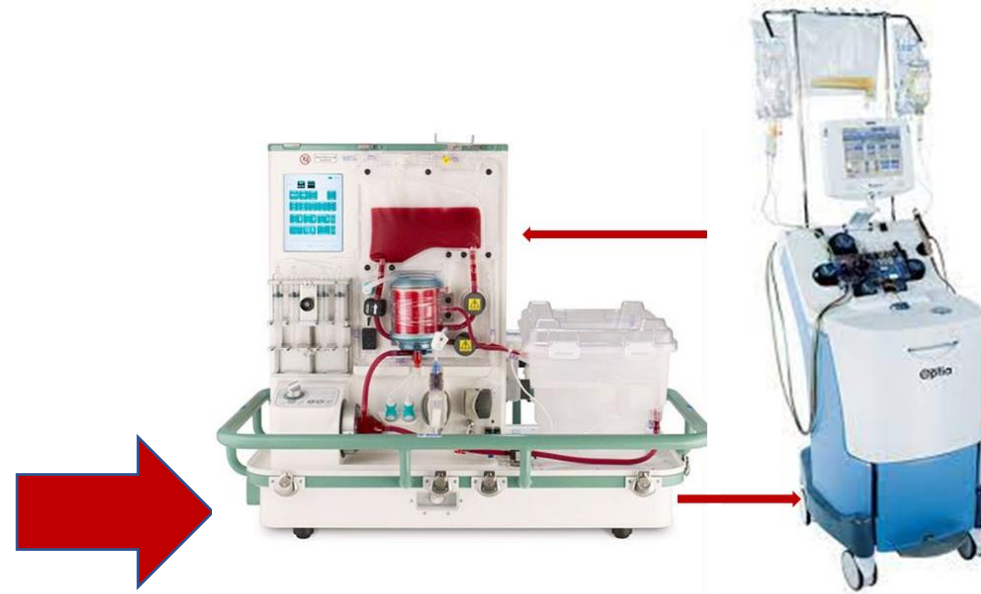
- Ex situ reperfusion **induces the release of DAMPs** from donor livers during NMP and subsequent reperfusion
- DAMPs released during perfusion **propagate injury causing ECD grafts to:**
 - **Function poorly** during NMP
 - Exhibit significant graft injury/ preservation reperfusion injury
- The aims of this study were to:
 - Assess the ability to **integrate Nucleocapture[®] technology** into the NMP ex-situ set up
 - Determine if **DAMPs can be removed from the perfusate** during NMP & subsequent ex-situ whole blood reperfusion on the circuit
 - Establish if the removal of DAMPs **reduced the magnitude of ex-situ reperfusion injury**

The set-up

NMP device (OrganOx metra)

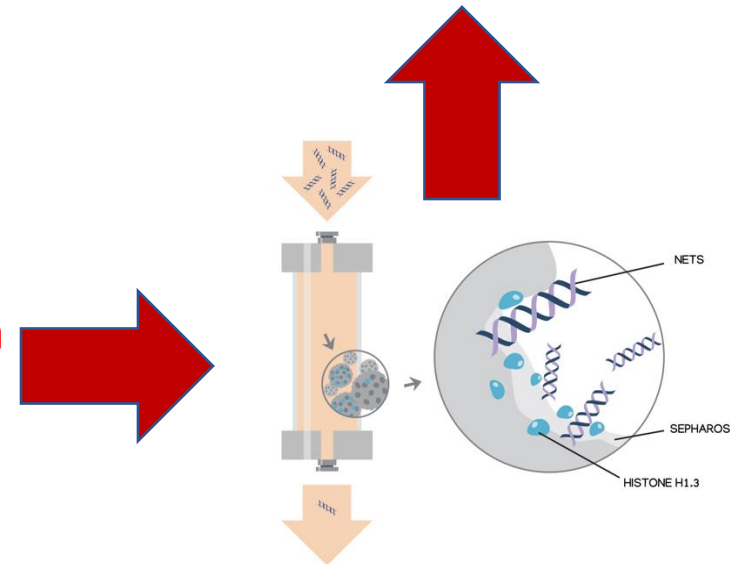
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Spectra Optia® Apheresis device (Terumo) with Classic NucleoCapture column (cNC), Santerus AG



OR

NucleoCapture hemoperfusion column prototype (hNC), Santerus AG



MECHANISM

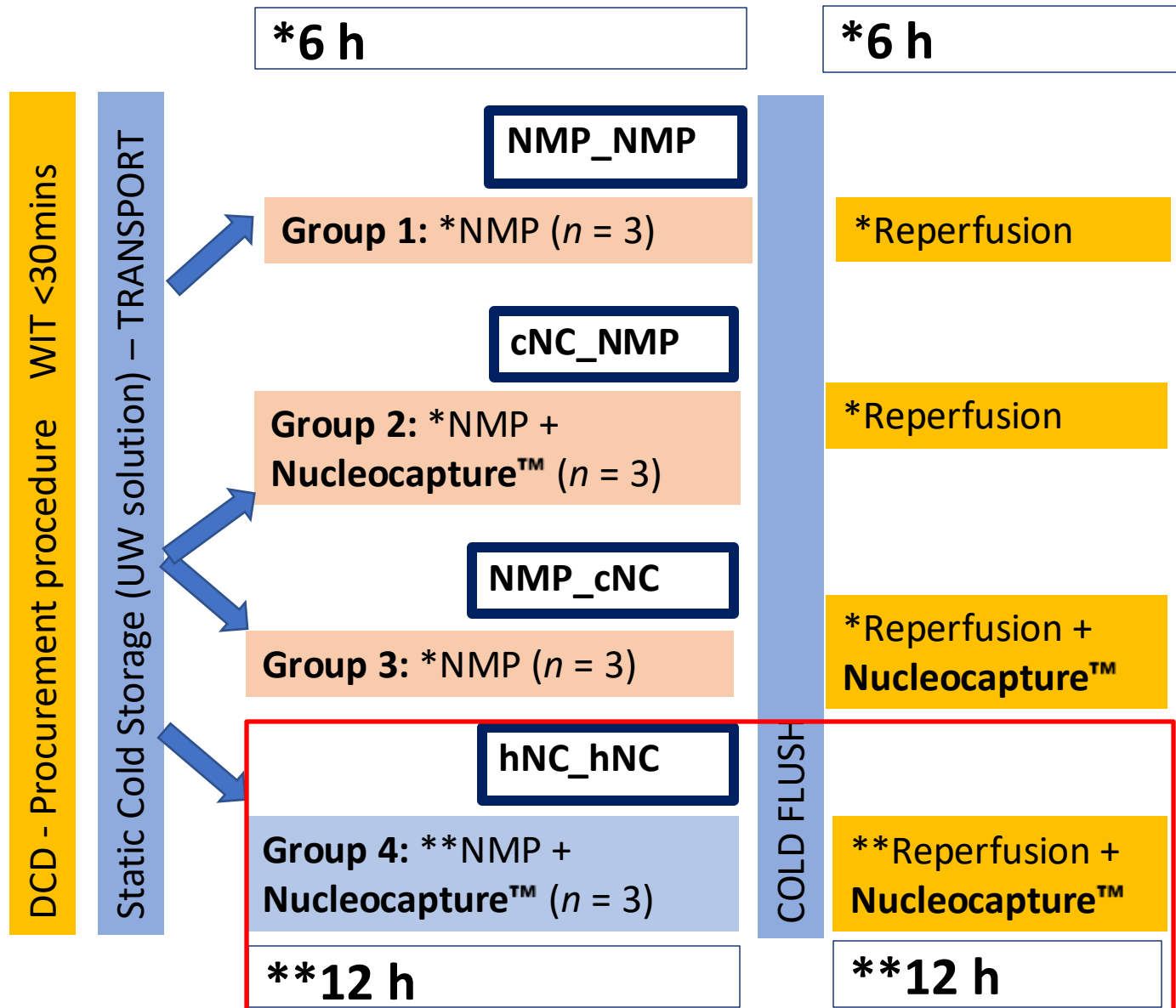
Binding via Linker histone H1.3

Specifically & tightly binds extracellular chromatin

REMOVAL OF DAMPS:

- Extracellular Histones
- Nucleosomes/NETs
- cfDNA & mito-cfDNA

Study design



- Total $n = 12$ DCD Pig livers
- 4 groups

2 Phases

- (1) **NMP** – Autologous RBCs and plasma (leukodepleted)
- (2) **Reperfusion** (whole blood allogenic (ABO matched))



Interventions:

- NucleoCapture during NMP or Reperfusion or Both Phases



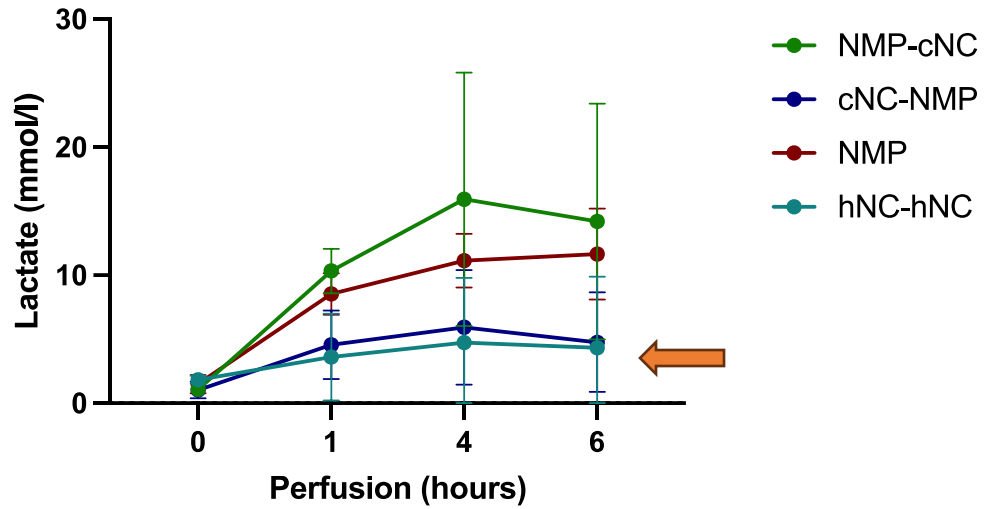
Outcomes/Readouts:

- Perfusion haemodynamics
- Lactate clearance
- Bile parameters (volume, pH, glucose)
- Perfusate Biochemistry
- Histology

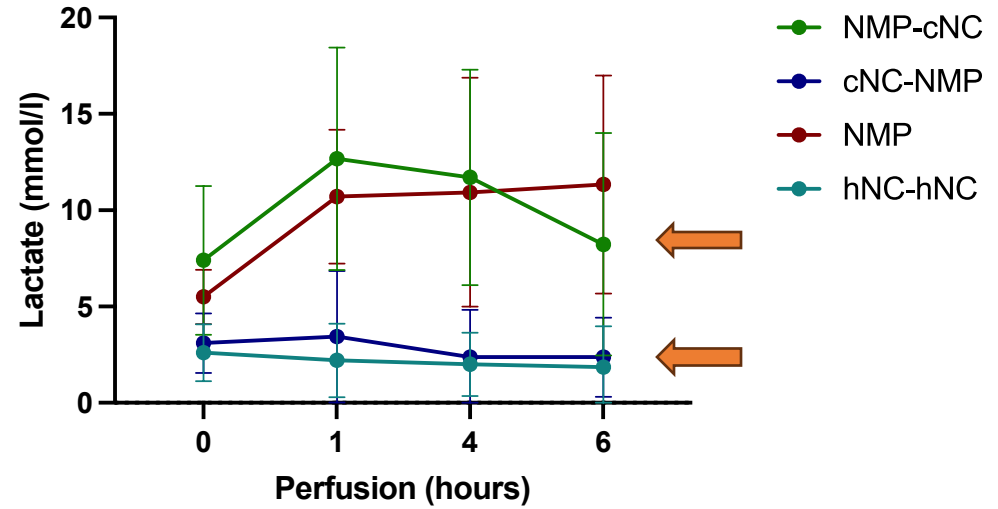


Results – Lactate clearance

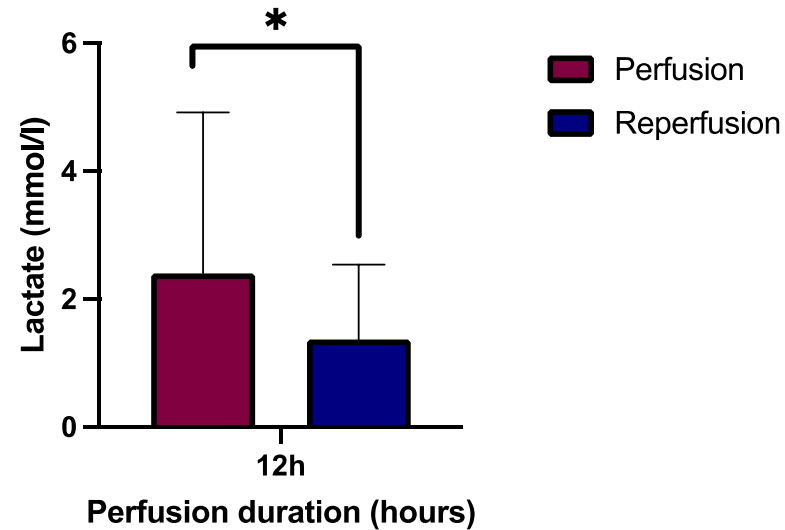
Lactate: Perfusion phase



Lactate: Reperfusion phase

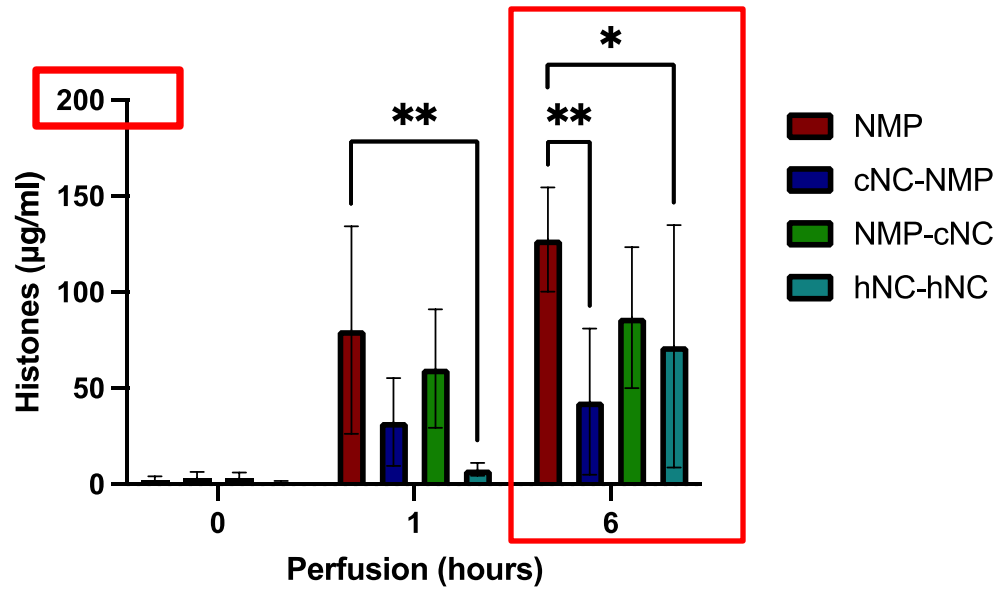


Perfusion vs. Reperfusion: hNC

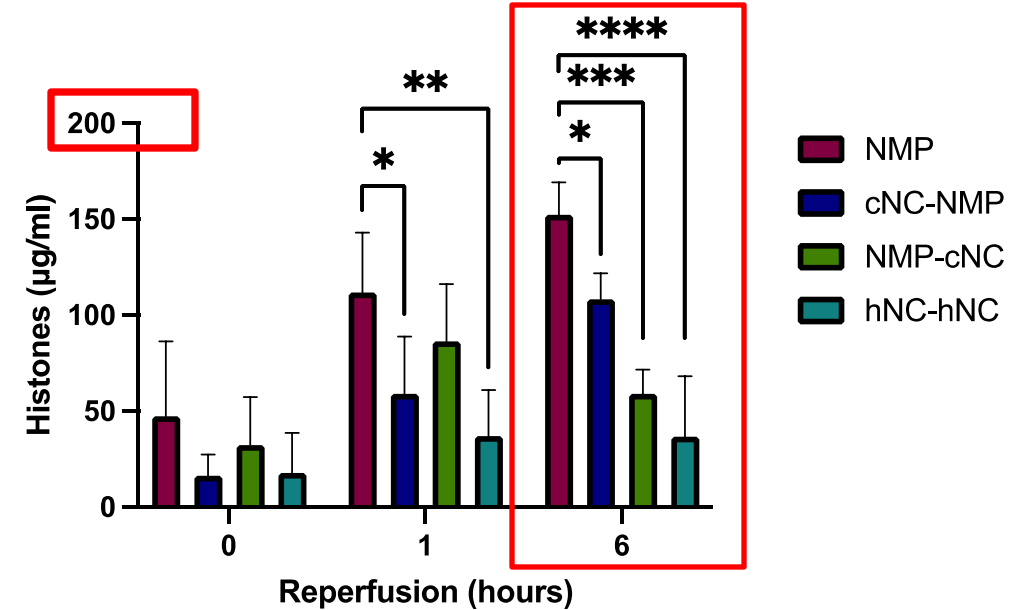


Results – Histone removal with NucleoCapture®

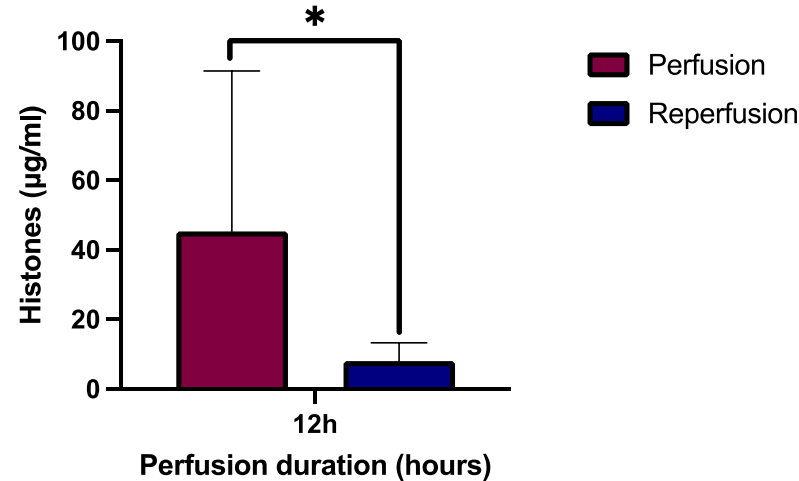
Extracellular histones: Perfusion phase



Extracellular histones: Reperfusion phase

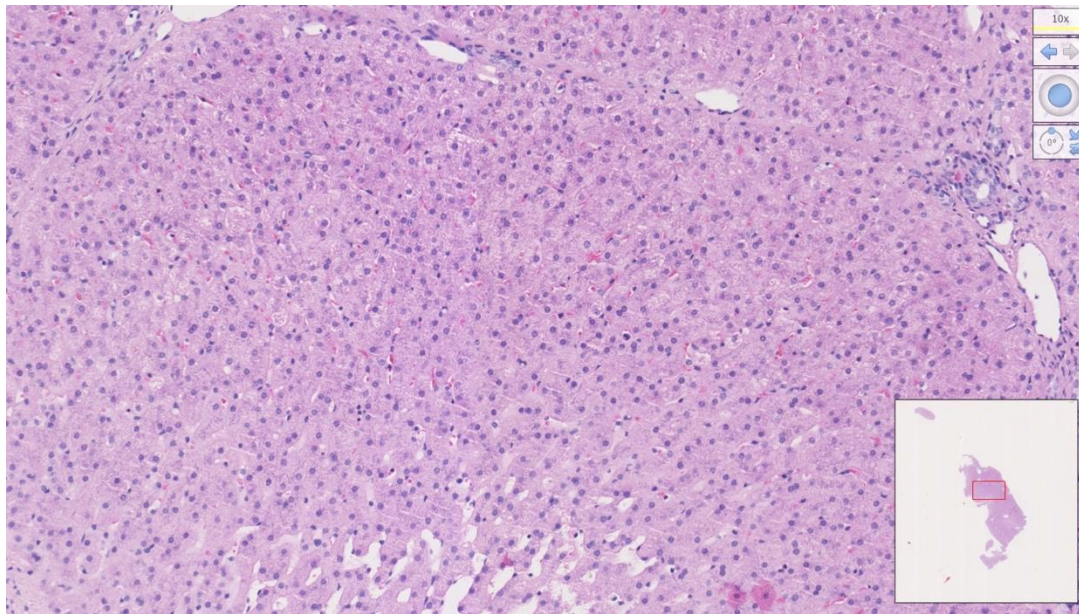


Extracellular histones: hNC

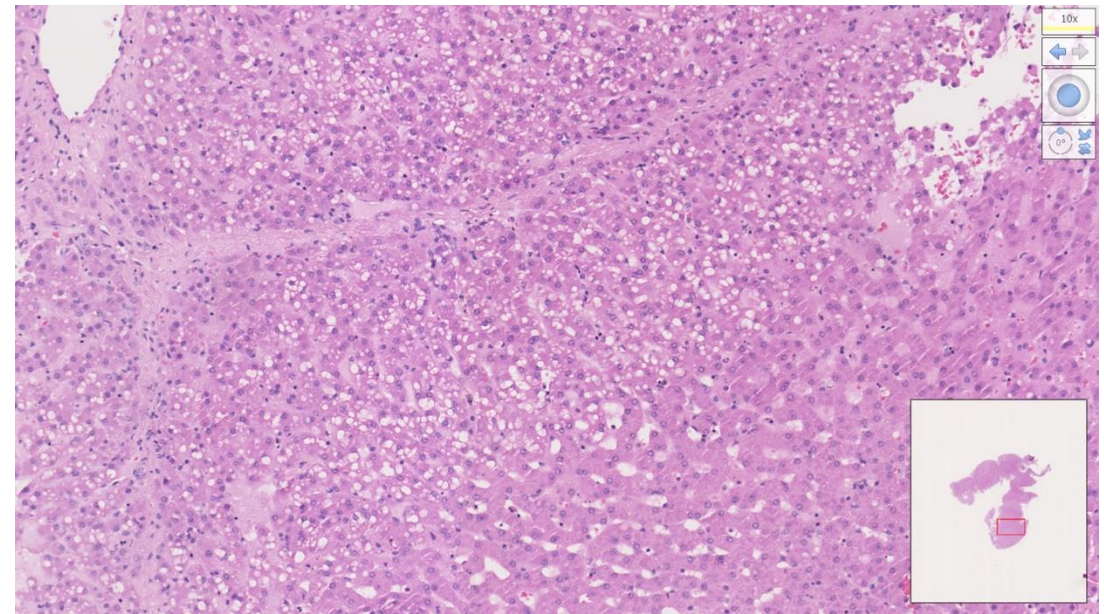


Results: Histology

No neutrophil infiltration at **end of initial NMP perfusion** with nucleocapture

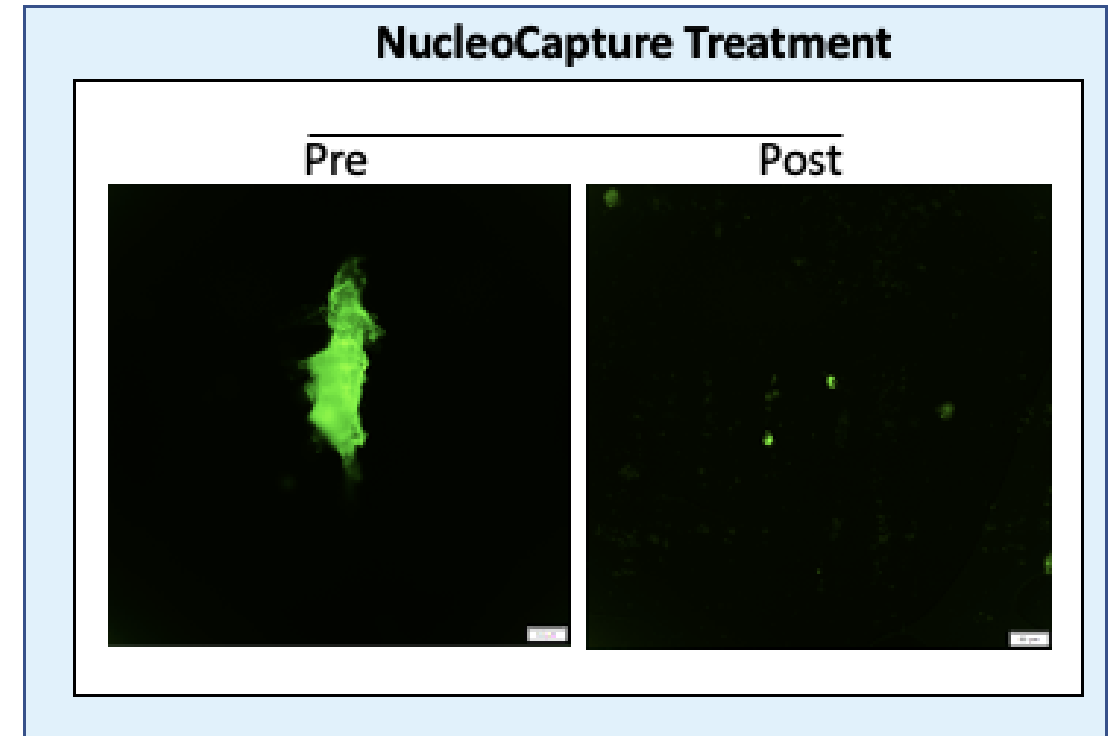
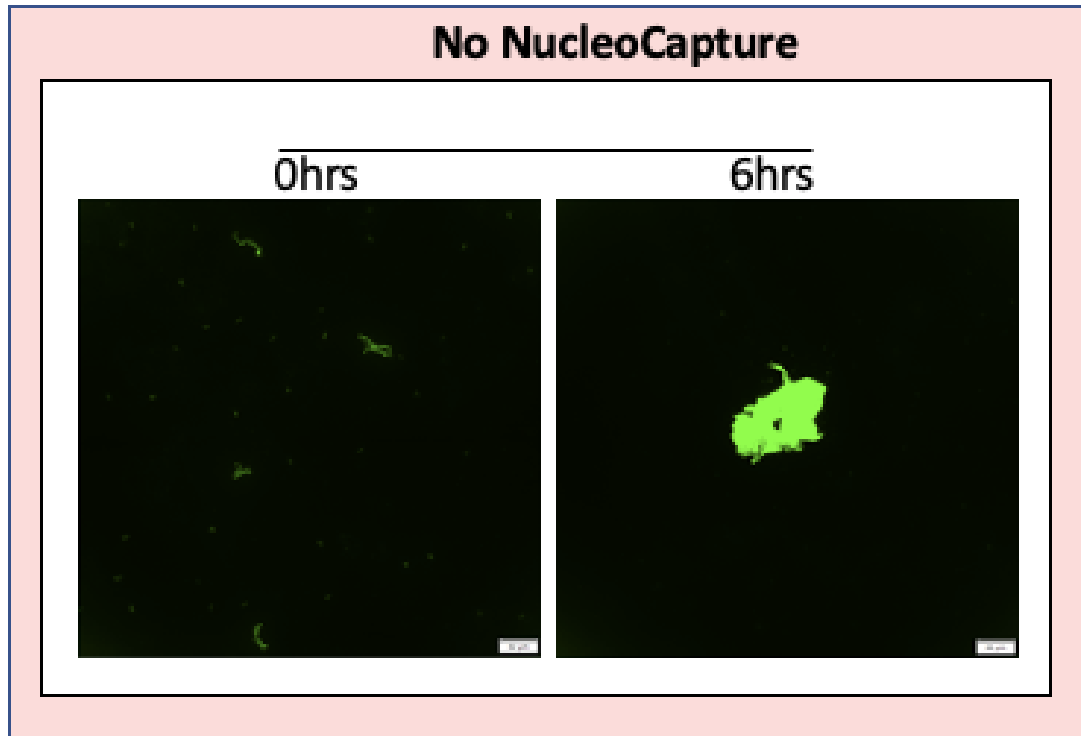


No neutrophil infiltration at **end of reperfusion** with nucleocapture



Results: Removal of microclots

Microclots were assessed by incubating samples with Thioflavin T and viewed under fluorescence microscopy. **NucleoCapture treatment resulted in a reduction in microclots ex-situ.**



Conclusions so far... & Limitations

- DAMP removal via Nucleocapture™ is achievable during both NMP and reperfusion by either connecting the spectra Optia device to the OrganOx *metra*™ device **OR** the continuous in-line NucleoCapture hemoperfusion column prototype
- Nucleocapture™ during initial NMP, i.e. employed to tackle ex-situ reperfusion induced by DAMPs in the circuit *seems* to have a beneficial effect on liver function during perfusion and also subsequent allogenic whole-blood reperfusion
- Limitations:
 - Size of groups
 - Ex-situ whole blood reperfusion - lack of 'true transplant' model
 - Functional readout – no porcine consensus
 - No discarded human liver perfusion

Thank you



Hussain Abbas: Hussain.Abbas@nds.ox.ac.uk

 @HussainAbbas_HK

Fungai Dengu: Fungai.Dengu@nds.ox.ac.uk

 @FDengu