Pump-Priming Grant

Report

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Nuffield Department of Surgical Sciences

Title: *Development and application of a large animal DCD model for the investigation immunomodulation of during normothermic machine perfusion of the liver.

Objective: The overarching objective of the study was to develop a platform for investigating specific approaches to the immunomodulation of donor organs during normothermic machine perfusion.

Questions: Can a large animal model re-create the passenger leukocyte kinetics observed in human organ NMP?
Does ex situ ischaemia reperfusion influence passenger leukocyte efflux and influx?

Method

We designed, optimised and implemented a slaughterhouse DCD multiorgan procurement method. Having established this, Porcine livers (N=4) procured using our protocol, were preserved with sequential static cold storage then NMP. During NMP, livers were subjected to repeated 20 min warm ischaemic hits (IHs) separated by 30mins of NMP. The perfusate was autologous leukodepleted red cells re-suspended in colloid. PLs in the perfusate were quantified using the Sysmex®cell counter system and samples stored for detailed flow cytometric analysis.

Results

The temporal kinetics of PLs during NMP-L in our porcine DCD model are the same as those observed in human livers during the COPE trial. Therefore, this is a valid large animal model for investigating this phenomenon with high translatability to the clinical setting.

During NMP, there is an inducible and reproducible efflux of PLs into the circuit that occurs in response to ischaemia reperfusion and is composed of predominantly lymphocytes with unexpectedly low numbers of monocytes. PL depletion during NMP may be feasible using an in-line leukocyte-filter upon ex situ reperfusion of donor livers.

Outputs (publications/presentations)

<u>Publications</u>

Journal: Annals of Translational Medicine (IF: 3.932) – Accepted

Abdominal Multiorgan Procurement from Slaughterhouse Pigs: A Bespoke Model in Organ Donation After Circulatory Death for Ex-Vivo Organ Perfusion compliant with the 3 Rs.
Fungai Dengu, Flavia Neri, Etohan Ann Ogbemudia, George Ebeling, Laura Knijff, Kathlyn Rozemberg, Richard Dumbill, Julien Branchereau1, Peter Friend, Rutger Ploeg, James Hunter

<u>International Presentations</u>

European Society of Transplantation (ESOT) biennial International Congress 2021 (Milan)

Brief Oral/e-Poster:

Ex situ ischaemia reperfusion mobilises Passenger Leukocytes into the circuit during liver normothermic machine perfusion.
Fungai Dengu, Tamsyn Clark, Hussain Abbas, Etohan Ann Ogbemudia, Faysal El Gilani, David Nasralla, Peter Friend, James Fildes
(Accepted)

American Transplant Congress (ATC 2020)
Poster (Scheduled for Philadelphia, USA)

Abdominal Multiorgan Retrieval from Pigs in a Slaughterhouse: A Reliable and Efficient Donation after Circulatory Death Model for Ex Vivo Organ Perfusion
F. Neri, **F. Dengu,** G. Ebeling, L. Knijff, K. Rozemberg, J. Branchereau, P. Friend, R. Ploeg, J. Hunter

British Transplant Society (BTS 2020)
Poster (Scheduled for Belfast, Northern Ireland)

Abdominal multiorgan retrieval from pigs in a slaughterhouse: a reliable and efficient donation after circulatory death model for ex vivo organ perfusion.
Mr Fungai Dengu, Dr Flavia Neri, Dr George Ebeling, Ms Laura Knijff, Ms Kathlyn Rozemberg, Dr Julien Branchereau, Prof Peter Friend, Prof Rutger Ploeg, Mr James Hunter

Local Presentations:

Nuffield Department of Surgical Sciences Away Day 2020, Selected for e-Poster.

Ex situ ischaemia reperfusion mobilises Passenger Leukocytes into the circuit during liver normothermic machine perfusion.
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(Accepted)

Next Steps (what is it leading to)

This work has enabled the development of multiple projects using the DCD slaughterhouse model exploring the delivery of various therapies (ranging from HIF modulators to liver regeneration inducers) to porcine livers during NMP as well as the development of a reperfusion model. Crucially it has allowed us to embark on immunodulation using extracellular vesicles as a delivery system for novel (RNA interference) therapies.

***Updated title: previous title had to be amended without significantly altering the overarching objectives of the study due to ill health of a collaborator and the inability to access the relevant material to directly address the previous question (i.e access dendritic/therapeutic cells)**