NIHR | Blood and Transplant Research Unit in Organ Donation and Transplantation at Cambridge and Newcastle Universities

Report from the Progress Meeting
held in Lecture Theatre 1.006, Urban Sciences Building, Newcastle University
on Wednesday 26 April 2023

The first progress meeting of 2023 for the NIHR BTRU in Organ Donation and Transplantation took place at the Urban Sciences Building in Newcastle on Wednesday 26 April 2023. There were over 60 attendees, including BTRU colleagues from Newcastle and Cambridge, and representatives from the Patient and Public Research Panel (PPRP), the Independent Steering Committee (ISC), NHS Blood and Transplant (NHSBT), the Faculty of National Experts (FNE) and the National Institute for Health and Care Research (NIHR), as listed below:

PPRP	Siân O'Dea (PPI Co-applicant), Pamela Denham, Irene Soulsby, Joan Bedlington, Roger Pape
ISC	Hilaria Asumu
NHSBT	Lorna Marson (NHSBT Lead for the BTRU), Rachel Johnson, Emma Lawson
FNE	Derek Manus (FNE Chair), Gurch Randhawa, Orin Lewis
NIHR	Rajinder Flora, Tom Hutchinson, Fiona Giles

The meeting included an update from the Deputy Director, research presentations from all theme leads, and updates on patient and public involvement and engagement (PPIE), industry collaborations and training. Each presentation was followed by time for Q&A.

DIRECTORS' UPDATE

BTRU Deputy Director Andy Fisher gave the Directors' update, starting with the key highlights from year 1 of the new unit:

- Good progress on short-term objectives in the research plan
- Completion of the 5-year PPIE strategy – glowing feedback from NIHR
- Successful launch meeting in Cambridge in October 2022
- National prizes and awards for BTRU researchers
- Successful site visit – positive feedback from NIHR and DHSC colleagues
- Major funding awards secured
- National leadership roles for senior BTRU investigators – ARCs
- First publications

He then elaborated on several aspects including the array of the prizes and awards secured by BTRU researchers, recent funding awards leveraged as a result of the BTRU award, and the national leadership roles for senior BTRU investigators in the development of organ assessment and repair centres (ARCs).

RESEARCH PRESENTATIONS

Research presentations from the main and cross-cutting themes were given by theme leads and theme researchers and covered recent progress in each theme. Individual projects, recent activity and/or future plans highlighted by each theme lead are listed below. [Links to theme overviews on the unit's website are also included.]

Main themes

Theme 1: Novel Perfusion Technologies – Chris Watson, Andy Fisher, Sarah Hosgood

Liver – Chris Watson
The presentation highlighted recent findings in the following liver perfusion/organ utilisation work streams:

- Normothermic regional perfusion (NRP) extends the acceptable withdrawal phase characteristics of donation after circulatory death (DCD) livers – no deleterious effects
- Alteplase successfully removes fibrin plugs and prevents cholangiopathy (damage to the bile ducts caused by inadequate blood flow) and probably other complications such as sinusoidal obstruction syndrome
- Donors with brain tumours are associated with a low risk of transmission in transplantation, even after major resection

Heart/lung – Andy Fisher
The presentation highlighted recent progress on the following heart/lung perfusion projects:

- Testing of a drug (CYM5442 – a selective S1PR1 agonist) that might reduce leaking of fluid from blood into donor lungs
- Preparation of stem-cell derived extracellular vesicles (EVs) to test on donor lungs and hearts as a potential treatment to reduce ischaemia reperfusion injury
- Investigation of cell-free DNA as a biomarker of donor lung injury, mitochondrial dysfunction and suitability for transplant
- Development of a score to quantify risk for any donor lung and recipient combination
- Testing of a drug that protects against COVID-19 using perfusion
- Demonstration that cold perfusion with oxygen of donor hearts leads to better function than simple cold storage

Kidney – Sarah Hosgood
The presentation highlighted recent progress on the following kidney perfusion projects:

- A clinical pilot study is being initiated to investigate the use of a cytokine filter in the normothermic machine perfusion (NMP) circuit to remove inflammatory mediators that are upregulated by the NMP process, with the aim of improving function after transplantation
- Investigation of prolonged perfusion periods using subnormothermic acellular perfusion (SNAP) suggests that SNAP is equivalent to perfusion with red blood cells with no adverse effects on perfusion parameters. Maintaining a kidney on a machine at normal body temperature and perfusing it with blood for long periods is difficult – SNAP may provide a suitable alternative
- Use of enzymes to change blood group antigens on kidneys shows 99% B antigen and 94% A antigen removal within a few hours under NMP conditions and 92% A antigen removal under hypothermic machine perfusion (HMP) – the next step is to test whether removal of the antigens is successful when perfusing in an incompatible environment
- Other ongoing studies: investigation of the reparative effects of neonatal kidney stem/progenitor cells (nKSPCs) during NMP of human kidneys with established ischaemic tubular injury; delivery of a novel fusion toxin protein (SYN002) that targets latent cytomegalovirus (CMV) in kidneys during acellular NMP with the aim of minimising or preventing CMV reactivation post-transplantation

Theme 2: Organ Donation and Utilisation – Colin Wilson
The presentation highlighted recent progress on the following projects:

- Investigation of extracellular vesicles (EVs) from kidney allograft microvasculature shows the EVs are pro-immunogenic and that increased organ damage = increased EV production
- Investigation of the amelioration of peribiliary plexus damage in DCD livers through complement inhibition using eculizumab

- NHSBT Registry analysis of liver transplant outcomes by ethnicity shows black recipients have poorer 1 year graft outcomes compared to white recipients and are more likely to have acute rejection at 3 months
- Investigation of micro RNA 21 (miR-21) as a target to inhibit the inflammatory response following ischaemic kidney injury
- Investigation of the impact of donor liver blood tests on liver transplant outcomes shows that livers from donors with raised transaminases can be accepted and transplanted with confidence, providing a safe, simple and immediate option to expand the donor pool
- Analysis of the impact of time to death (TTD) in DCD liver transplantation shows TTD does not have a linear relationship with graft outcome
- Ongoing development of the ORQA (organ quality assessment) digital decision-making tool for point of donation organ assessment – pilot interface for scoring images showcased at the British Transplantation Society congress; final stages of governance approvals are underway to receive NHSBT image dataset

Theme 3: Improving Long-term Outcomes – Vasilis Kosmoliaptsis

The presentation focused specifically on the work streams aimed at reducing transplant immunological risk: molecular human leukocyte antigen (HLA) mismatch and antibody–HLA profiling

- Molecular HLA mismatch
  - A major study has been completed in adult kidney transplantation describing a novel HLA molecular mismatch algorithm (HLA ASSESS) that can be used as a biomarker of primary alloimmunity risk
  - Work is underway with NHSBT to apply HLA ASSESS to predict long-term kidney graft outcomes utilising the NHSBT transplant registry to examine whether molecular HLA mismatch can be incorporated into the kidney allocation policy
  - Future work will include a randomised controlled trial (RCT) to examine the utility of molecular HLA mismatching to identify kidney transplant patients for immunosuppression minimisation
- Antibody–HLA profiling
  - A study has been completed describing (development and validation) of a novel assay, microfluidic antibody affinity profiling (MAAP), and its implementation (proof-of-principle) for HLA-specific antibody profiling – MAAP is the first assay to allow the simultaneous quantification of antibody concentration and antibody affinity in an aqueous phase
  - A study has been completed describing the importance of quantifying alloantibody affinity and concentration in the assessment of clinically relevant HLA-specific antibodies in transplantation
  - A study is ongoing focusing on how MAAP may be applied to improve immunological risk assessment in transplantation
  - Future studies will include work on delisting unacceptable HLA antigens to improve access to transplantation in highly sensitised patients

Cross-cutting themes

Theme 4: National Registry Analysis and Health Data Science – Gavin Pettigrew

- There was a reminder of three main aims of national registry analysis: (i) to improve patient awareness and promote patient engagement with transplant process; (ii) to support the introduction of new technologies; (iii) to inform the design/development of clinical trials
- Dominic Summers and an MPhil student (Dr Roberts) are analysing registry data linked to postcode for listed recipients to investigate the factors determining waiting time to transplantation and why an apparent inequity in access to transplant among centres persists despite national allocation factors

- There have been discussions with Prof Exley (Theme 6) about applying for additional funding to link registry analysis with inequity of access to transplantation including whether all listed kidney transplant recipients should have the option to receive offers of fast-track kidneys – only about half of UK centres are enrolled, so for a substantial proportion this is not an option
- Plans are ongoing for a feasibility study of uncontrolled DCD donation – France and Spain have undertaken >1000 uDCD kidneys transplants in the last 5 years and although there are higher rates of primary non-function for uDCD vs extendend criteria donors (ECDs) in the UK, long-term survival is much better than ECDs
- An NIHR EME grant application has been submitted for a prospective trial of withdrawal of immunosuppression in transplant recipients prior to autumn COVID/flu booster vaccination

Theme 5: Genomics and Biomarkers – Menna Clatworthy

- There was a brief reminder about how this cross-cutting theme works across the three main themes and across all organs: Theme 1 – to determine whether interventions delivered during perfusion have improved the organ; Theme 2 – to determine whether the organ is good enough to transplant; Theme 3 – to determine whether the immunosuppressant has worked
- The following recent studies were highlighted:
  - Use of a cell filter in the circuit during ex situ liver perfusion reduces inflammatory and fibrosis gene expression and increases interleukin 24 (IL24)
  - Investigation of clazakizumab as a potential treatment for late antibody mediated rejection (ABMR) in kidney showed that it induces detectable changes in peripheral blood transcriptome and downregulates immune signatures including antibody-effector pathways – the blood signatures may reflect changes in the kidney
- Other ongoing projects include:
  - Predictive biomarkers for outcomes in kidney transplantation (donation after brain death (DBD) v DCD): n=300 DBD biopsies requested from quality in organ donation (QUOD) biobank in Nov 2022
  - Predictive biomarkers for outcomes in liver transplantation – transcriptional profiling of QUOD liver biopsies (n=80): data have been generated and analysis is underway (Chris Watson, Vas Kosmoliaptsis)
  - Investigating transcriptional changes in interleukin 6 (IL6) blockade in chronic ABMR in kidney transplantation (Georg Bohmig)
  - Natural killer (NK) cells and killer-cell immunoglobulin-like receptor (KIR) genotypes in kidney transplant outcome (Olivier Thaunat)
  - Biopsies pre- and post-heart perfusion (Marius Bermann)

Theme 6: Applied Health Research and Inequalities in Transplantation – Cath Exley

- Following an introduction from the theme lead, Ben Rimmer gave a progress update on the following work stream: Assessing quality of life in solid organ transplant recipients – a systematic review of the development, content, and quality of available patient-reported outcome measures (PROMs)
- The aim is to obtain a synthesised understanding of the development, content and quality of existing quality of life (QoL) PROMs for solid organ transplant recipients
- Comprehensive database searches have identified 79 papers reporting 55 QoL PROMs which will be critically examined to determine quality and appropriateness for use
- The most suitable PROMs to refine and pilot with different groups of solid organ transplant recipients will be identified
- The findings will be valuable to researchers and the clinical community – appropriate PROM selection is essential for effective supportive care

PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT (PPIE) UPDATE

The PPIE update was opened by Siân O'Dea (PPI Co-applicant and Patient and Public Research Panel (PPRP) panel member) who spoke about the importance of communication. She highlighted three key points for researchers when involving patients and the public in their work: (i) use simple day-to-day language; (ii) explain technical terms (analogies can be particularly useful here); and (iii) keep sentences short (particularly in written work, such as plain English summaries and other research documentation).

Deputy Director Andy Fisher then gave the rest of the PPIE update on behalf of PPIE Lead Hannah Murray who was unable to join the meeting. The PPRP continues to support the unit with a current membership of 14. This includes five new members who have joined within the last 6 months, which has increased the diversity of membership, one of the key aims of the new unit. A PPRP terms of reference document has been agreed and published on the website and there is continued support and training for panel members, including regular well-being check-ins. Owing to increased demand for panel feedback on research proposals, the panel meetings have recently changed from quarterly to monthly. Those panel members who wish to be remunerated are paid in line with NIHR guidance.

Work is also underway on the impact evaluation initiative which aims to develop a strategy to assess and evaluate the impact of PPI on BTRU research. Plans for the pilot study have been refined, integrating feedback from colleagues, with the next step being identification of projects from both Newcastle and Cambridge sites to participate.

Community engagement has been very strong in year 1, with BTRU representation at numerous in-person events including New Scientist Live, Engage FMS SciScreen (Newcastle University), Cambridge Festival, Big Biology Day and Mini Medical School. There are also regular online events including the seasonal get-togethers and Research Explained webinar series.

Siân Russell (Theme 6) highlighted the forthcoming Talking Spaces event on Saturday 20 May, which involves a walk along the coast from Whitley Bay to South Shields followed by a lunch. Talking Spaces is new BTRU initiative aimed at finding informal environments where people can feel at ease discussing organ donation and transplantation (ODT). She encouraged BTRU colleagues at all levels to attend.

PPIE plans for year 2 were then outlined, including further Talking Spaces events, a new art project to explore individual journeys through ODT, annual online training on the UK Standards for Involvement, delivery of the annual MRes in Transplantation PPIE lecture, and further engagement events. More engagement with community groups and collaboration with national and international partners are also included in plans for the coming year.

Any researchers requiring PPI input for their research, or support with PPIE activities, were encouraged to contact Hannah directly: hannah.murray@newcastle.ac.uk.

INDUSTRY COLLABORATION UPDATE

Industry Lead Bill Scott presented an update on the unit's ongoing work to maintain and develop industry collaborations. He gave a reminder that the unit had committed to working 'with patients, public and *industry* to develop a comprehensive research platform that facilitates rapid translation of new developments into clinical practice'. As reported at the launch meeting last year, new collaborations already established under this BTRU include Avivo Biomedical (blood group enzymes), Astra Zeneca (therapies to treat ischaemia reperfusion injury), Synklino (cytomegalovirus (CMV) studies), Altavant Sciences (consultancy), Sanofi (consultancy) and Meliohealth (collaboration on immune signature in chronic

lung allograft dysfunction). In addition, a collaboration with SAS analytics is supporting development of an artificial intelligence (AI) approach to grading chronic injury on renal biopsy.

TRAINING UPDATE

Professor Neil Sheerin (BTRU Training Lead), Beth Gibson (Post Doc, Newcastle) and Serena MacMillan (PhD Student, Cambridge) gave a brief overview of the hugely successful training event for early career researchers that had taken place the day before the progress meeting. There was wide participation from both sites, including research assistants, technicians, PhD students and post docs. The main focus of the day was PPIE, with a keynote welcome presentation from Professor Gurch Randhawa, Professor of Diversity in Public Health at the University of Bedfordshire, who discussed tackling ethnic and faith inequalities in organ donation in the UK and examining the role of public involvement. This was followed by an introduction to PPIE from BTRU PPIE Lead Hannah Murray and PPIE round table discussions between the early career researchers and a number of patient/public contributors. Trainees were then given the opportunity to present their work in a way that was accessible to a non-scientific audience. The day concluded with a number of careers talks from a variety of speakers: Lizzie Withington, Company Creation Manager at Newcastle University; Ryan Wolstenholme, Programme Manager from NIHR; and Dr Auriane Destrument, a Freelance Scientific Translator from Destrument Translations. Initial verbal feedback from participants had been overwhelmingly positive, with the round table discussions seen as a particular highlight. Further feedback would be gathered by electronic survey, with the results being used to inform future training events within the BTRU.