Institution: University of Sunderland

Unit of Assessment: UoA3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Expanding the donor pool for kidney transplantation

1. Summary of the impact

Research undertaken with the Newcastle Hospitals Transplant Unit led to the approval of two new transplant processes and resulted in the expansion of the kidney donor pool.

- A new device, assisting with efficient peritoneal cooling, was created and adopted for the retrieval of human kidneys for transplant from Category II donors; it improved the functional quality of these kidneys post-transplant for recipient patients at Sunderland Royal Hospital between 2007 and 2010. The research has informed EU policy through its inclusion in the recent draft of 'ESOT recommendations for DCD kidney transplantation'.
- Since 2012, kidneys removed due to small renal tumours are available for transplant into new recipients after their *ex vivo* resection, resulting in clinical intervention and a new procedure adopted. Previously, these excised kidneys were not available for transplant.

2. Underpinning research

There are around 7000 patients on the organ donor waiting list, while there are about 2000 organs available for transplant, with an obvious mismatch in supply and demand. Those who do not receive a transplanted organ either remain on the waiting list, or become too ill to receive an organ, resulting in many deaths. Research since 2004 at the University of Sunderland, led by Dr Noel Carter and Dr Anne Cunningham (until 2011, now at Universiti Brunei Darussalam), developed technologies that have been utilised to expand the human donor pool. [1] Two different aspects of this research resulted in positive impacts on kidney transplant patients.

Initial work focused on increasing the success of Category II organ retrieval. Under the Maastricht criteria, unsuccessful resuscitation of cardiac patients leads to Category II donors; next-of-kin consent is required for the resultant donations, listed as 'Uncontrolled' Donation after Cardiac Death. During the period when consent is sought, the restricted blood flow to organs causes a shortage of oxygen and glucose required for cellular metabolism, resulting in ischaemic injury and decreased function after transplantation. Research carried out by several clinical and doctoral students, in collaboration with Professor David Talbot (Consultant Transplant Surgeon, Freeman Hospital, Newcastle upon Tyne, and Visiting Professor at the University of Sunderland), led to the design and development of a new device for *in situ* cooling of the peritoneal cavity, in collaboration with regional company, Acrol. Insertion of dialysis fluid into the peritoneal cavity and its flow through a cooling unit using a peristaltic pump before returning it to the peritoneal cavity resulted in an improved method for the retrieval of functional kidneys from Category II donors.

Animal studies demonstrated that, together, *in situ* perfusion and the newly developed peritoneal cooling offered a more rapid and substantial decrease of renal temperature and slower build-up of renal lactate levels compared to *in situ* perfusion alone. [1,2,3] The method was translated into a full scale human clinical retrieval procedure by Prof Talbot and the device achieved ethical approval for local use in 2007. During 2007-2010, several transplant procedures were carried out using the device; it was retired from service when the UKT funding for Newcastle Category II organ transplants ended in 2010, although it remains a viable option for this class of donor.

Subsequently, research has focused on the use of kidneys with small tumours, which were previously discarded after removal. Excision of the tumours and *ex vivo* resection of the kidneys allows transplant into new recipients, e.g. those with a high risk of mortality due to the lack of potential donor kidneys. Sunderland's focus has been on the role of immunosuppressant drugs and the post-transplant treatment strategy. Issues can arise from any undetected carcinoma in the renal tissue, as the standard procedure of immunosuppressant therapy with cyclosporin inhibits the natural suppression of carcinoma regrowth by the immune system. The research investigated the immunosuppressant strategy required to suppress tumour growth following transplantation of a carcinoma-bearing kidney into an animal model system. It was found that the use of an immunosuppressant with antineoplastic activity, such as sirolimus, maintained the health of the

transplanted kidney, while suppressing carcinoma regrowth. [4] It was also noted that in sirolimus-treated animals, there was significantly less tumour growth when a poorly matched donor kidney was used, which encouraged the natural immune regulation of neoplastic growth.

The impact of this research has wider applicability than to renal transplantation alone and is being used to inform to liver and heart transplantation procedures. [5] Complementary research evaluated the attitudes of young British adults to organ transplant donation and identified policy implications for enhancing the donor pool. [6]

Under the guidance of Dr Carter and Prof Talbot, six PhD students contributed to this research; in particular, Dr Alex Navarro (2006 – 2010) was largely responsible for the studies on peritoneal cooling and Muhammad Khurram (2012 – ongoing) is carrying out the current work on renal cell tumours. Others who have contributed to this research area are: Dr Mettu Reddy (2006 – 2010); Dr Soroush Sohrabi (2006 – 2010); Dr Aimee Kibondo (2006 – 2011); and, Chris Ray (2009 – 2013, submitted).

3. References to the research

The key publications in relation to this work are as follows:

1. A.P. Navarro, S. Sohrabi, M. Reddy, **N. Carter**, A. Ahmed, and **D. Talbot**. (2008) Dual transplantation of marginal kidneys from non-heart beating donors selected using machine perfusion viability criteria. *Journal of Urology*, **179**(6): 2305; discussion 2309. *The combined long-term function of dual transplant organs considered sub-optimal at transplantation was found to be comparable to the function of a single renal graft with good function at transplantation. Dr Carter provided the crucial molecular biology scientific input that evaluated and assured the viability of the kidneys for transplant. It has been cited in publications from Belgium, Poland and the USA, demonstrating its global relevance.*
2. A.P. Navarro, J. Ashera, S. Sohrabia, M. Reddy, S. Stamp, **N. Carter**, and **D. Talbot**. (2009) Peritoneal Cooling May Provide Improved Protection for Uncontrolled Donors After Cardiac Death: An Exploratory Porcine Study. *American Journal of Transplantation*, **9**: 1317. *In this paper*, e*vidence was presented that supported the use of peritoneal cooling to reduce damage to the organs of Uncontrolled Donors after cardiac death through the study of organ performance after transplantation into pigs. Dr Carter provided the molecular biology expertise to quantify the protection offered by this method. The citations in publications from the UK and Netherlands (including a review of methods from Maastricht for preserving kidneys from cardiac death donors) demonstrate its international significance.*
3. C. H. Wilson, H. Wyrley-Birch, D. Vijayanand, A. Lee, **N. Carter**, M. Haswell, A. Cunningham, and **D. Talbot**. (2012) The Influence of Perfusion Solution on Renal Graft Viability Assessment. *Transplantation Research*, **1**: 18. *Research evidence is presented that intraperitoneal cooling and the use of HTK preservation fluid reduce ischemic injury and that the choice of a kidney for donation should take into account its preservation method since donor death. Dr Carter provided the molecular biology evidence for this project. A Netherlands publication on the donation of other organs cited this work, demonstrating its reach to alternative applications.*
4. M.A. Khurram, D. Rix, **D. Talbot**, and N. Soomro. (2011) Transplantation with kidneys removed electively for renal cell carcinomas. *Transplant International*, **24**(S1: Suppl 2): 55. *This abstract summarises the rationale for using tumour-bearing kidneys for transplant into different recipients; it was delivered as an short oral presentation at the European Society for Organ Transplantation (ESOT) in Glasgow in 2011 and followed by a full oral presentation at ESOT in Vienna in September 2013, during which the evidence for a sirolimus post-treatment strategy was presented. Dr Carter was a co-author of the 2nd presentation.*
5. M.A. Khurram, A.O. Sanni, D. Rix, and **D. Talbot**. (2011) Renal Transplantation with Kidneys Affected by Tumours. *International Journal of Nephrology*, Volume 2010, Article ID 529080. *This review brings together the evidence from various international studies showing that the use of tumour-bearing kidneys for transplantation can be hugely*

successful and offers an additional pool of potential donor organs for high risk patients on kidney dialysis. It informed our subsequent research on post-transplant treatment to identify the optimal strategy for success.

6. L. Coad, **N. Carter**, and J. Ling. (2013) Attitudes of Young Adults from the UK Towards Organ and Tissue Donation and Transplantation. *Transplantation Research,* **2**: 9. *To ensure that the research remains relevant and acceptable to patients, a questionnaire-based investigation examined the attitudes of young adults to donation and transplantation. Although young adults are generally in favour of transplant, few are registered for organ donation. Implications for policy to enlarge the future donor pool are discussed. Dr Carter contributed scientific expertise in organ and tissue transplantation. The findings have international applicability across the range of donor organs for transplantation.*

The research leading to the impact outlined here has been funded by a variety of sources and receives continued funding for future impact aims. Funding of £69,225 has been awarded to Dr Carter from industrial, charity and government sources (2007-current) and Dr Cunningham received £17,138 from NHS and charitable sources (2003-2010) while at the University of Sunderland.

4. Details of the impact

The research carried out at the University of Sunderland has resulted in the following impacts:

- the adoption of two new processes through device and method development;
- a clinical intervention leading to much improved outcomes for two groups of patients;
- the informing of clinical guidelines for solid organ donation;
- an increase in public awareness of method development in solid organ transplantation;
- the career development of highly skilled researcher/practitioners for specialised medical roles.

The research resulted in the design and development of a device for rapid peritoneal cooling, which was implemented alongside the standard *in situ* perfusion method for clinical transplant procedures for Category II donors. The clinical use of this device allowed a larger pool of potential donors to be accessed than with traditional methods. The process was approved by the Sunderland Hospitals Ethics Committee in 2007 and subsequently adopted into practice. The research findings had immediate impact on 10 retrieval procedures from Category II donors, as a result of which 20 transplants were made during 2007-2010. The retrieval surgical work was carried out at Sunderland Royal Hospital by Prof Talbot of the Liver, Renal and Pancreatic Transplant Unit at the Freeman Hospital in Newcastle upon Tyne. The outcome for the patients is enormous, besides their improved quality of life, their survival has been made possible, as it is unlikely that these patients would have received transplants if this procedure had not been made available at that time.

During this original research there were several national and local news reports on the improvements to transplant success using this procedure (detailed in Section 5), which have improved public awareness of transplantation and have also augmented recognition of Dr Carter's contribution to transplant research.

Further research conducted by Dr Carter in Sunderland, in collaboration with renal transplant specialist Prof Talbot, examined the post-transplant regrowth of renal carcinoma tissue in an animal model and identified a suitable treatment to suppress its growth, while also suppressing rejection of the renal graft. The dual action of sirolimus in this context offers an improved outcome for the use of kidneys with carcinoma tissue and enhances the possible donor pool for kidney transplant patients; additionally, it has application to the transplant of other organs and the related donor pools, which is of international relevance. Dr Carter's research also showed a better suppression of carcinoma regrowth alongside the suppression of graft rejection was achieved when less well-matched kidneys were used for transplant. This interesting observation further enhances the potential donor pool, by increasing the number of 'matching' kidneys for transplant.

These new results have already informed clinical intervention with four cases of transplantation

during 2013. In three of these cases, small renal carcinomas were confirmed in the donors' kidney following radical nephrectomy; in the fourth case, the tumour was found to be benign after *ex vivo* inspection. After *ex vivo* resection, all four kidneys were transplanted into four high-risk patients, who were either unlikely to be placed on the waiting list due to other co-morbidities (and hence unlikely to be given another opportunity for a transplant organ), or were more likely to respond slower to organ transplant from a living donor. These procedures were carried out at the Freeman Hospital in Newcastle by Prof Talbot; three were reported to be good functional grafts, signalling an improvement in the outcome for these patients. This approach is being adopted into practice at the Freeman Hospital in Newcastle and is being promoted internationally at conferences.

The research carried out here will have a lasting impact on future transplant procedures and clinical guidelines. Already, the peritoneal cooling procedure has informed EU policy through its inclusion in the European guidelines for Donation after Circulatory Death (DCD) 'ESOT recommendations for DCD kidney transplantation', which were developed in March 2013. These guidelines are used to inform the UK guidelines; hence, the work will also inform the latest HTA Code of Practice 2: Donation of Solid Organs for Transplantation, for which Parliamentary approval will be sought in early 2014. It has also supported the career development of highly skilled researchers who have gone on to take specialist roles. One PhD graduate is now employed by Nottingham University Hospitals NHS Trust as a trainee consultant surgeon in the field of organ transplant and another secured a post as a trainee consultant surgeon in the transplant unit within the London Postgraduate School of Surgery.

5. Sources to corroborate the impact

1. The research described here was carried out in collaboration with a renal transplant expert from the Freeman Hospital, Newcastle upon Tyne (also Visiting Professor at the University of Sunderland). Supporting statements include '*The work……with the University of Sunderland has addressed donors after cardiac death and kidneys that were affected by tumours*,' and *Therefore the cooperation between University of Sunderland and the Newcastle Transplant programme has been beneficial for transplant patients for the North East and through National and International presentations and publications to the Transplant community as a whole'.*

2. Other endorsements of the adopted processes and patient outcomes have been provided by the Directorate Manager for the Institute of Transplantation, Newcastle upon Tyne NHS Foundation Trust. Feedback was sought from the donors and recipients; one statement received from the coordinator read '*The recipient has subsequently written to the donor – an experience the donor relates as "moving and emotional"*.'

3. The 2013 draft European guidelines for Donation after Circulatory Death (DCD) 'ESOT recommendations for DCD kidney transplantation' highlighted the inclusion of peritoneal cooling: '*In an animal study, the renal temperature was significantly lower with ISP [*in situ *perfusion] in addition to normal cold intravascular flush.*' The document refers to Navarro *et al*., 2009. [ref 2 above]

4. Approval of the initial animal model research was granted by the Newcastle and North Tyneside Research Ethics Committees, stating '*ethical approval is now granted in respect of this research study application*', and approval for the peritoneal cooling device was awarded by the Sunderland Hospitals Ethics Committee for use in the local area. The local coroner also stated '*I have no concerns about the procedure you have mentioned*'.

5. Two news stories highlighted the transplant success stories at the University of Sunderland. The first relates to the *in situ* peritoneal cooling of kidneys, while the second shows that the technology is applicable to other organs.
   a. 12 Jul 2010: http://www.sciencedaily.com/releases/2010/07/100709083749.htm [accessed 17th Nov 2013];
   b. 10 July 2013: http://www.itv.com/news/tyne-tees/2013-07-10/new-machine-could-double-number-of-heart-transplants/ [accessed 17th Nov 2013].