Vision science and translational researcher Professor Keryn Williams gives an insight into current corneal transplant procedures and describes the path that steered her to this field.

Could you first provide an overview into your background, explaining what led you to study transplantation immunology and how this directed you to your career in ophthalmology?

My first postdoctoral position was in the Nuffield Department of Surgery at the University of Oxford, UK. My head of department there was an Australian surgeon, Professor Peter Morris, who was establishing a new renal transplant programme in the Thames Valley about the time I arrived. It was a very exciting place to be, and those of us who worked on the laboratory side of the department relished the task of trying to master transplantation immunobiology in order to help the clinical staff as much as possible.

After six years, it was time to return to Australia, and Professor Morris suggested to me that I might like to join the new Department of Ophthalmology being established at Flinders University. The Foundation Professor there, Douglas Coster, asked me to inject some science into what he described as 'the art of corneal transplantation'. These two surgeons have been wonderful mentors to me over my entire scientific career. It’s impossible to overemphasise the impact of expert, visionary and kind mentors in the career of any scientist.

With whom do you collaborate and to what extent has a multidisciplinary approach proven important to the success of your projects?

Evidence suggests that collaborative research often has the biggest impact. We all collaborate widely, both nationally and internationally. For myself, I suppose in one sense my most important collaboration is with the 700-odd Australian ophthalmologists in a variety of academic and private practices who have so willingly provided a wealth of de-identified information on the outcomes of corneal transplantation in their patients over many years. Provision of this information is entirely voluntary, and it’s just extraordinary that they support the Australian Corneal Graft Registry (ACGR) so graciously.

The benefit of a multidisciplinary approach is that it brings together researchers who have completely different skill-sets and ways of thinking about problems. The synergies are quickly apparent to all involved. Some of my most enjoyable and productive interactions have been with chemists and material scientists – who would have thought?

The goal of translational research – which forms a large part of your research portfolio – is to transform basic biomedical research discoveries from bench to bedside. What are the major challenges of such targeted research?

Translational research often takes an inordinate amount of time to yield outcomes of practical use. The pipeline from discovery to patient benefit can amount to a decade or more. For knowledge translation, the major difficulty after retrieving and disseminating the evidence lies in measuring changes in the pattern of practice.

Can you describe the advantages of using an evidence-based approach to measure outcomes in patients with eye disease?

The advantages are the same for any set of patient outcomes, whatever the disorder or disease: the best outcomes will be linked to therapeutic approaches that actually work. Some ineffective treatments may do no actual harm, but the individual may then
be denied a proven treatment that would have improved his or her health. Ineffective treatments are sometimes also quite expensive and waste scarce resources. Some, frankly, can be dangerous.

Although not a problem in Australia specifically, the need for human cornea donors worldwide far exceeds supply. Do you envisage a time when a corneal xenograft may be possible?

We flirted with corneal xenografts in experimental models many years ago, but found that they underwent rapid rejection. I am not particularly optimistic about the potential of full-thickness corneal xenografts, however beguiling the idea may be in theory. Despite this, I do think there may be some potential for partial thickness xenograft materials to supplement the use of human corneas.

Could you outline your research objectives for the next five to 10 years?

One of the aims of our centre has always been to promulgate the tenets of evidence-based ophthalmology as much as possible. In the past we’ve run workshops at which we’ve discussed the hierarchy of evidence, demonstrated efficient retrieval of scientific literature, summarised statistical methodologies and presented the evidence for and against topical and contentious issues of practice. For the future, we are contemplating a different model, making much more use of online, web-based material.

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Researchers at Flinders University, South Australia, have made significant impacts on ophthalmology, establishing new care and data facilities together with their cutting-edge research into the eye.

CORNEAL TRANSPLANTATION WAS one of the first transplant surgeries to have been successfully performed; unfortunately, it has also proven one of the hardest to perfect in relation to long-term graft survival. The cornea is a unique tissue, with a very high density of nerve endings but no blood supply, and has classically been considered to enjoy a degree of immune privilege. Although one might expect these qualities would make it less vulnerable to damage by the immune system, in fact about 30 per cent of full-thickness corneal grafts undergo rejection.

Inflammation and neovascularisation also predispose towards corneal allograft failure, which affects around 10 per cent of transplants in the first few years. In the long-term, the results are even less encouraging, with fewer than half of all corneal grafts surviving past 15 years. On top of this, the procedure requires tissue from deceased donors, producing a long waiting list in some jurisdictions. Even so, 1,500 Australians require corneal graft surgery every year either to restore vision or relieve pain – after all, transplantation is still the premier treatment for corneal opacity, globally the second-leading form of blindness.

CHANGING THE GAME

One team of researchers headed by Professor Keryn Williams, leader of Flinders University’s Research Centre for Ophthalmology, Eye and Vision and Scientific Director of the Australian Corneal Graft Registry (ACGR), has significantly altered this picture in Australia. In addition to the ACGR, the Eye and Vision Centre has established and maintains a number of other ophthalmological registries including the Australian and New Zealand Registry of Advanced Glaucoma, the Registry of Advanced Diabetic Retinopathy, and the Australian and New Zealand Ophthalmic Surveillance Unit, all of which have a strong influence on clinical practice.

Since arriving at Flinders in 1981, Williams and her collaborators have been responsible for radical improvements, not only to knowledge in the field of ophthalmology, but also to the facilities and best clinical practice available to patients in need of corneal transplant or treatment for numerous other diseases of the eye.

In 1982, the new Department of Ophthalmology was responsible for establishing both Australia’s first formal eye bank and its first ophthalmology

Registering an interest

In May 1985, Professor Keryn Williams founded the Australian Corneal Graft Registry (ACGR), collecting de-identified information on human corneal transplants from all over Australia. After almost 30 years of operation, the Registry now contains records of more than 27,000 transplants – and is therefore an invaluable resource for clinicians.

The idea of the Registry was based on the success of others established for vascularised organ transplantation, including the one championed by Williams’ mentor Professor Peter Morris for kidney transplants. “The utility of these registries was obvious, and we thought that such an approach might also be very useful for corneal transplantation,” Williams recalls.

Around 700 ophthalmologists participate in the programme, supplying initial information at registration about the recipient, donor, operative procedure and practice of the eye bank, and then follow-up data at annual intervals until the graft is lost or the death or loss-to-follow-up of the patient. The information is then checked for consistency and added to the Registry’s database, before ultimately being subjected to detailed analyses and compiled into a regular report.

Today, the ACGR is probably the largest repository of clinical corneal transplantation data in the world – and it certainly contains the most sustained patient follow-ups. It serves as a model for those establishing new registries around the world.
INTELLIGENCE

RESEARCH IN THE DEPARTMENT OF OPHTHALMOLOGY

OBJECTIVES

To improve graft survival and visual outcomes for patients who require corneal transplants to restore vision or relieve pain.

KEY COLLABORATORS

Associate Professor Richard Mills; Professor Jamie Craig; Professor Justine Smith; Associate Professor Celia Chen; Associate Professor Sonja Klebe; Dr Miriam C Keane; Dr Rachel Galettis, Flinders University, Australia

Staff of the Eye Bank of South Australia, Flinders University, Australia

The many Australian ophthalmologists who contribute information to the Australian Corneal Graft Registry, Flinders University, Australia

FUNDING

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Ophthalmic Research Institute of Australia

DonateLife (Australian Organ and Tissue Donation and Transplantation Authority)

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PROFESSOR KERYN WILLIAMS is Leader of the Research Centre for Ophthalmology, Eye and Vision at Flinders University, Australia, as well as being Scientific Director of the Australian Corneal Graft Registry (ACGR). Williams conducted her PhD at the University of Melbourne, Australia, before undertaking postdoctoral research at the University of Oxford’s Nuffield Department of Surgery, UK, where she developed her interest in transplantation immunobiology. On her return to Australia, Williams joined the new Department of Ophthalmology at Flinders University. She founded and is Scientific Director of the ACGR and is NHMRC Principal Research Fellow at Flinders University.

One promising route to improved graft survival being pursued by Williams and her colleagues is that of gene therapy, which involves transferring genes into the donor corneal tissue prior to transplantation.

In recent years, the Flinders team has published a number of papers making excellent use of the ACGR database in order to guide clinical practice and inform research. These studies have revealed the heightened risk of graft failure when using corneas transported by air-freight from other states over locally-sourced tissues, as well as the increased danger, in patients with bilateral corneal grafts, of rejection episodes in one eye following rejection in the other. An increased understanding of paediatric graft survival, long-term graft survival in penetrating corneal grafts for keratoconus, and lamellar versus penetrating keratoplasty have all been achieved from mining this valuable source of information.

FUTURE PLANS

One promising route to improved graft survival being pursued by Williams and her colleagues is the field of gene therapy, which involves transferring genes into the donor corneal tissue prior to transplantation. Using an ovine model, the researchers have already demonstrated that this method of immunomodulation can significantly prolong corneal graft survival. Their subsequent aims are to characterise, construct and test lentiviral vectors for the effective delivery of these therapeutic genes. The scientists theorise that it might be possible to extend allograft survival indefinitely, provided that multiple transgenes in the donor cornea are able to target several pathways of potential graft damage.

Williams and the scientists working alongside her at the Flinders Department of Ophthalmology have had an incalculable influence on the pursuit of this clinical science in Australia, as well as dramatically improving the patient outcomes clinicians are able to achieve. Although there is still much to learn – as Williams admits: “Corneal transplantation still falls well short of its therapeutic potential” – the researchers are indefatigable in their work, and if their past achievements are any indicator of future performance, this gap may well be closed in the future.

Key facts

• The cornea is the transparent window at the front of the eye which, if damaged, can cause blindness

• Corneal damage is the second leading cause of blindness worldwide

• Every year 1,500 Australians need a corneal transplant, with all graft donations coming from human eyes

• 90 per cent of corneal grafts survive for one year, but fewer than 50 per cent survive longer than 10 years

day-surgery unit, increasing the availability of ophthalmologic procedures as well as donor tissues. 15 years later, Flinders scientists published a paper demonstrating for the first time that advanced donor age made little difference to graft success. As a result of this discovery, which has been duplicated in the US and elsewhere, corneal donations became far more abundant in Australia.

DATA MINING

The research being conducted at Flinders’ Department of Ophthalmology ranges widely, covering topics related to clinical practice in the treatment of many diseases including retinopathy, macular degeneration and glaucoma, as well as less prevalent but equally troubling conditions such as eye diseases of newborns, intraocular infections and diseases of the ocular surface. Helping to reduce the burden of blindness and corneal disease by improving corneal transplant procedures, however, is still an enduring priority for Williams and her group; towards this end, much of the work they undertake involves drawing conclusions from ACGR data.

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