npg

Surgical strategies to improve visual outcomes in corneal transplantation

MS Rajan[1,2]

Abstract

The recent years have brought about a sea change in the field of corneal transplantation with penetrating keratoplasty being phased to newer lamellar keratoplasty techniques for a variety of corneal pathology. Improved and innovative surgical techniques have allowed selective replacement of diseased host corneal layers with pre-prepared healthy donor corneal lamellae for anterior corneal disorders such as keratoconus and posterior corneal disorders such as Fuch's corneal endothelial dystrophy. The results of lamellar techniques are encouraging, with rapid visual rehabilitation and vastly reduced risk of immune-mediated transplant rejection. The techniques of deep anterior lamellar keratoplasty and Descemet's stripping endothelial keratoplasty (DSAEK) continue to evolve with advent of femtosecond lasers and newer concepts such as pre-conditioned donor corneas for Microthin DSAEK and Descemet's membrane keratoplasty. This review describes the current developments in lamellar keratoplasty, including the futuristic approach using cell therapy to restore vision in corneal blindness.

[1]Cornea Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK

[2]Vision and Eye Research Unit (VERU), Anglia Ruskin University, Cambridge, UK

Correspondence:
MS Rajan, Consultant Ophthalmologist, Cornea Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS trust, Hills Road, Cambridge CB2 0QQ, UK.
Tel: +44 (0)1223 257 168;
Fax: +44 (0)1223 274 810.
E-mail: madhavan.rajan@addenbrookes.nhs.uk

Introduction

Corneal organ transplantation remains the mainstay treatment for patients with corneal blindness. Until recently, penetrating keratoplasty has been the gold standard for rehabilitating patients who had lost their corneal transparency to infection, degeneration, or dystrophy.[1] Penetrating keratoplasty (PK), which involves whole-organ transplantation, has inherent problems related to multiple sutures, high degrees of induced astigmatism, increased risk of endothelial rejection, and poor long-term graft survival.[2–4] All these factors limit early visual recovery and compromise long-term visual stability in patients undergoing penetrating keratoplasty. Therefore, recent years have seen considerable improvements in techniques to overcome such limitations. Current developments in lamellar keratoplasty have enabled partial-thickness corneal transplants to selectively replace anterior or posterior corneal tissue depending on the type of pathology in order to allow early visual rehabilitation and long-term stability.[5,6] This article aims to describe the present trends in lamellar keratoplasty and future strategies such as cell therapy that are being developed to address the growing demand for corneal transplantation.
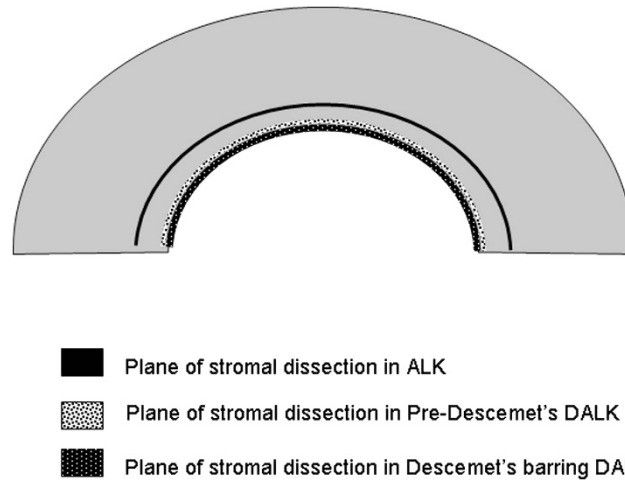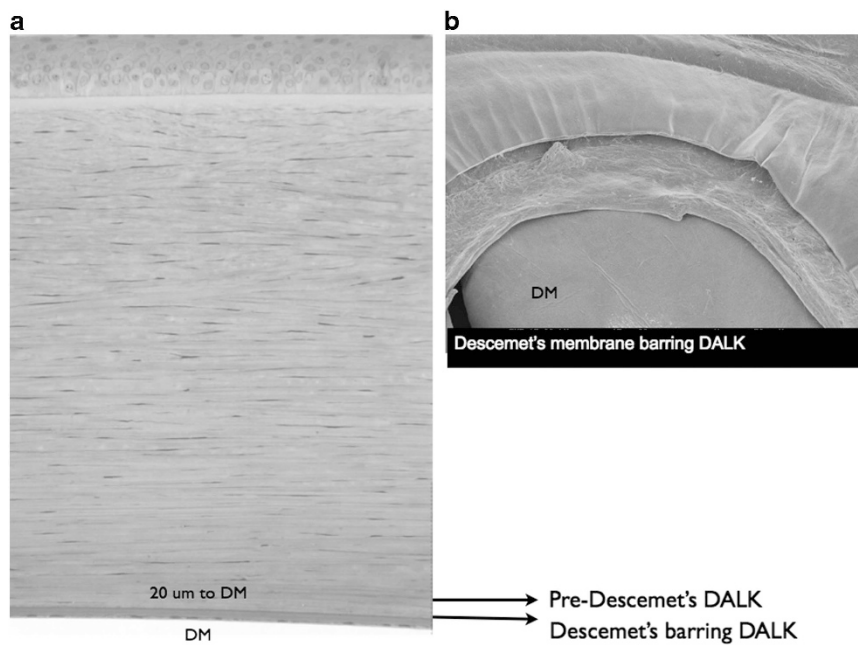
Lamellar keratoplasty

Anterior lamellar keratoplasty (ALK) involves removal and replacement of the corneal stroma with preservation of the host endothelial layer, which provides long-term protection from immune-mediated endothelial rejection. Although ALK has been practiced for several years, recent innovations have allowed total debulking of the corneal stroma in order to improve visual outcomes following the procedure (Figure 1).[6–8] Previous studies involving partial or subtotal removal of the corneal stroma for pathologies such as keratoconus and stromal dystrophies had not provided full visual recovery, although they

Plane of stromal dissection in ALK

Plane of stromal dissection in Pre-Descemet's DALK

Plane of stromal dissection in Descemet's barring DALK

Figure 1 Schematic diagram of human cornea in a cross-section showing the stromal plane of dissection in Anterior lamellar keratoplasty (ALK), Pre-Descemet's deep anterior lamellar keratoplasty (DALK), and Descemet's barring DALK.

a

b

DM

Descemet's membrane barring DALK

20 um to DM

DM

→ Pre-Descemet's DALK
→ Descemet's barring DALK

Figure 2 Histophotograph of a human cornea showing (a) deeper stromal planes of dissection in Descemet's and Pre-Descemet's DALK, and (b) a scanning electron microscopy image of bare Descemet's membrane (DM) with a smooth interfacing surface.

were successful in retaining the host endothelium. The stroma–stroma contact, interface scarring, and excessive recipient host stroma were all implicated in poor visual recovery in ALK. In comparison, the deep ALK (DALK) procedures developed by Anwar and Melles have paved the way for total or near-total separation of the corneal stroma from the underlying Descemet's membrane by the Big Bubble technique or air-assisted deep lamellar dissection.[7,8] Although Descemet's barring procedures are technically challenging, pre-Descemet's dissection appears to achieve comparable visual and refractive results to penetrating keratoplasty, provided the residual recipient (host) stroma is no more than 20 um (Figure 2).[9,10] These visual results were substantiated by a report by the American academy, in which 11 published studies comparing DALK with PK were analyzed.[11] In addition, the graft survival of DALK corneal transplants was shown to be higher at 97% at 5 years compared with 73% for penetrating keratoplasty in a separate study.[12] Thus, current trends favor DALK procedures over PK for corneas with

stromal pathology and healthy host endothelium, with proven advantages of comparable visual and refractive results to those of PK with improved long-term graft survival.

Femtosecond-assisted keratoplasty

Femtosecond lasers have practically replaced microkeratomes for lamellar cuts in LASIK surgery. Similarly, femtosecond lasers have been used to perform vertical and deeper cuts to facilitate PK with variously shaped profiles to configure better wound apposition and reduce post-op astigmatism.[13,14] Top hat, reverse hat, mushroom, zig-zag, and christmas tree-shaped excisions have been tested with moderate improvement in post-op astigmatism.[15] Recently, femtosecond lasers have been utilized to standardize the DALK procedure with some success.[16,17] Developments in laser energy, repetition rate, and cutting profiles are likely to improve deeper ablations to improve DALK procedures, and it is likely that femtosecond lasers will have an important role in the future of corneal lamellar transplantation with an aim to achieve stronger graft–host interface, early suture removal, and reduced induced astigmatism.[6]

Posterior lamellar keratoplasty

Endothelial keratoplasty has replaced PK as the gold standard procedure for corneal endothelial dysfunction.[18] The surgical technique originally termed deep lamellar endothelial keratoplasty has undergone significant improvements in surgical techniques to achieve selective replacement of the diseased endothelium with a functional endothelial layer (Figure 3).

DSAEK

The most commonly practiced procedure is Descemet's stripping automated endothelial keratoplasty (DSAEK), in which a posterior donor lamella prepared with an automated microkeratome is inserted after stripping the host Descemet's membrane.[19] There are several advantages compared with PK, which includes reduced post-op astigmatism, rapid visual recovery, and improved graft survival.[18] Graft detachment and primary graft failures in DSAEK show specific trends compared with PK. During the learning curve, post-op detachment and primary failure were reported to be between 5 and 80% and 3 and 29%, respectively.[18,20] Current studies show improving trends in both of these complications, with groups reporting less than 10% risk of post-op graft detachment and a 5–8% risk of primary graft failure.[20] Surgeon experience and better tissue handling techniques have contributed to the improved DSAEK outcome. In DSAEK, mean endothelial density loss appears to be between 13 and 54% in the first 6 months.[21,22] Graft rejection episodes following DSAEK are fewer compared with PK and were typically reported as being between 10 and 12% at 2 years.[23]
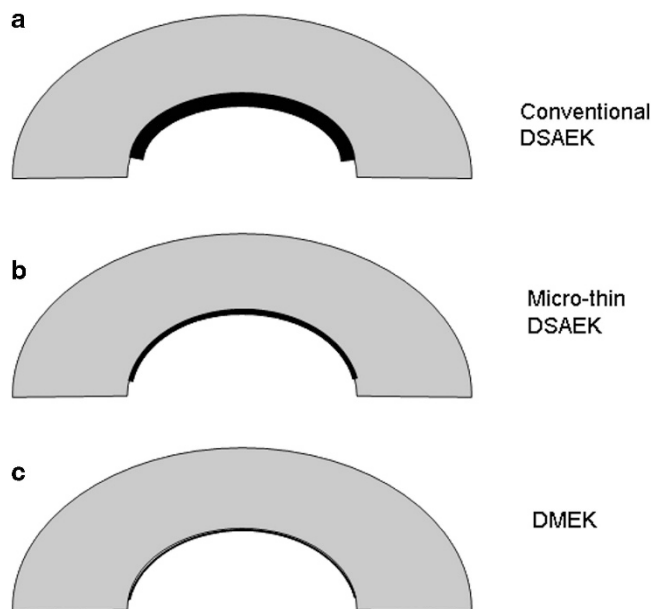
Figure 3 Schematic diagram of the human cornea in a cross-section showing the three surgical methods in endothelial keratoplasty with varying graft thicknesses at 170 microns in (a). Descemet's stripping automated endothelial keratoplasty (DSAEK) compared with 80 microns in Micro-thin DSAEK (b) and 20 microns in Descemet's membrane endothelial keratoplasty (DMEK) (c).

Thin DSAEK

Recent developments in endothelial keratoplasty have focused on techniques to standardize the thickness of endothelial grafts.[24,25] Graft thickness in DSAEK has been reported to vary between 50 and 250 μm.[26] Endothelial graft thickness directly influences the posterior radius of the curvature and, as per thick lens equation, increases the focal length, thereby decreasing the refractive power of the cornea.[27] This leads to the hyperopic shift observed in all reported DSAEK series, and with increased stromal content there are implications to interface irregularities and risk of allograft rejection.[20] The above factors potentially decrease full visual recovery, and in order to address this problem thin DSAEK techniques are becoming increasingly popular.[28,29] Current techniques to achieve thin endothelial grafts include the use of two microkeratome passes with a motorized microkeratome (Ultrathin DSAEK) and a Micro-thin DSAEK.[29] The main limitation to achieving a thin DSAEK graft is the variability in thicknesses encountered in human donor corneas in culture. Cadaveric human donor corneas both in organ culture and cryopreservation demonstrate increased thickness due to stromal swelling, which in turn leads to variable thickness of posterior lamella endothelial grafts for a constant thickness of anterior lamella removed during microkeratome dissection. We recently reported a technique to successfully achieve significantly thinner DSAEK grafts by controlling the thickness of donor corneas by utilizing pachymetry-controlled stromal dehydration before microkeratome dissection (Micro-thin DSAEK).[29] The airflow device (CAMflow) utilized for stromal dehydration is shown in Figure 4. These techniques improve the predictability of achieving sub 100 μm endothelial graft thickness resulting in increased percentage of eyes reaching their full visual potential.

DMEK

Transplantation of Descemet's membrane and endothelium in Descemet's membrane endothelial keratoplasty (DMEK) has shown excellent visual results and totally avoids the stromal content being transplanted into the host eye.[30–32] This technique is currently limited by its surgical complexity in graft preparation and handling, with an increased detachment rate reported between 58 and 92%.[20,32,33] However, with accruing center expertise this is currently showing an improving trend, and recent reports are between 18 and 20% of post-op air injections and decreasing trend in primary graft failure.[20] Perhaps the most exciting aspect of DMEK apart from full visual recovery is the significant reduction in graft rejection episodes reported at 1 year,
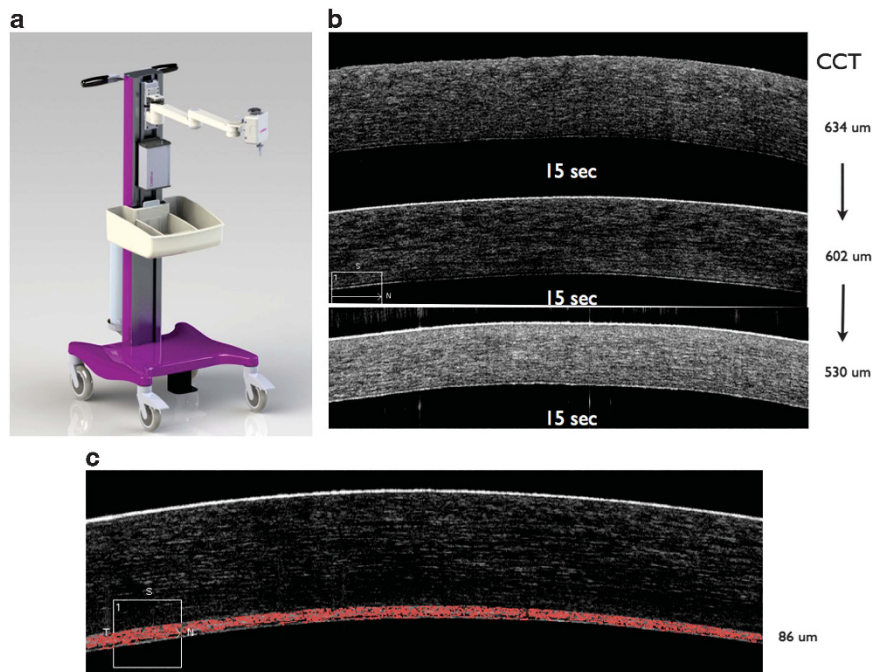
Figure 4 (a) The CAMflow airflow device for pachymetry-controlled stromal dehydration for Micro-thin endothelial keratoplasty; (b) rapid reduction in stromal thickness to target central corneal thickness (CCT) of 530 μm with 15 s increments of sterile airflow followed by a single microkeratome pass using a 350 μm cutting head in the preparation of sub 100 μm micro-thin endothelial grafts (c).

but this will need to be substantiated with longer follow-up.[34] DMEK surgery is likely to have a vital role in the future, and with better techniques many more corneal surgeons are likely to adapt to this procedure to rehabilitate patients with endothelial decompensation.

Corneal endothelial cell therapy

The visual threshold for surgical intervention in corneal endothelial diseases has changed markedly in recent years with techniques such as DSAEK, thin DSAEK, and DMEK.[20–35] As a consequence, the demand for human cadaveric corneas has risen, with nearly 40% of 40 000 corneal transplants comprising endothelial procedures in the United States alone between 2009 and 2010.[20] Graft failures and redo endothelial procedures further add to the demand of eye banks around the world.[36] In order to address the demand, emphasis has been placed on ex-vivo cultivation of human corneal endothelial cells (HCECs) and transplantation of the cultured endothelium to recover corneal transparency.[37] HCECs are arrested at the G1 phase of the cell cycle and it has been shown that HCECs have the potential to proliferate in response to growth stimulation factors.[38] Recent reports highlight the effect of Y-27632, a specific inhibitor of the Rho-associated coiled-coil forming kinases (ROCKs) in promoting adhesion and proliferation of monkey CECs.[39] Further, FGF-2 stimulates cell proliferation of HCECs through degradation of p27Kip1 (p27).[40] There is increasing laboratory evidence that the proliferative potential of HCECs could be reactivated for ex-vivo cultivation toward clinical transplantation into the eye, as a substitute for the present versions of endothelial keratoplasty. Current research is focused on optimum cell-culture conditions, evaluation of functional potential, and methods for cell delivery.[41–44] Cell therapy for corneal diseases has significant potential in addressing future demand for human cadaveric corneas and could possibly have an important role in replenishing endothelial cell density in failing corneas.

Conclusions

In summary, lamellar keratoplasty techniques have revolutionized the field of corneal transplantation with significant improvements in visual, refractive, and graft survival outcomes. Although PK still has a vital role in a subset of patients, in severe corneal compromise early surgical intervention with lamellar keratoplasty in clinical conditions such as Keratoconus and Fuch's corneal dystrophy has resulted in the paradigm shift observed in recent years. With increasing demand for cadaveric human corneas, there needs to be focused attention on improving organ donation campaigns and research into cell therapy, in particular for corneal endothelial diseases, both of which are vital to the overall strategy to identify potential solutions for corneal blindness in the future.

Conflict of interest

Mr Rajan developed the CAMflow device for Micro-thin DSAEK in collaboration with Network Medical Ltd, UK.

References

1 Keenan TD, Carley F, Yeates D, Jones MN, Rushton S, Goldacre MJ. Trends in corneal graft surgery in the UK. *Br J Ophthalmol* 2011; **95**(4): 468–472.

2 Han DC, Mehta JS, Por YM, Htoon HM, Tan DT. Comparison of outcomes of lamellar keratoplasty and penetrating keratoplasty in keratoconus. *Am J Ophthalmol* 2009; **148**(5): 744–751.

3 Williams KA, Muehlberg SM, Lewis RF, Coster DJ. Influence of advanced recipient and donor age on the outcome of corneal transplantation. Australian Corneal Graft Registry. *Br J Ophthalmol* 1997; **81**(10): 835–839.

4 Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. *Am J Ophthalmol* 2005; **139**(2): 311–319.

5 Tan DT, Dart JK, Holland EJ, Kinoshita S. Corneal transplantation. *Lancet* 2012; **379**(9827): 1749–1761.

6 Tan DT, Mehta JS. Future directions in lamellar corneal transplantation. *Cornea* 2007; **26**(9 Suppl 1): S21–S28.

7 Melles GR, Lander F, Rietveld FJ, Remeijer L, Beekhuis WH, Binder PS. A new surgical technique for deep stromal, anterior lamellar keratoplasty. *Br J Ophthalmol* 1999; **83**(3): 327–333.

8 Anwar M, Teichmann KD. Big-bubble technique to bare Descemet's membrane in anterior lamellar keratoplasty. *J Cataract Refract Surg* 2002; **28**(3): 398–403.

9 Ardjomand N, Hau S, McAlister JC, Bunce C, Galaretta D, Tuft SJ *et al.* Quality of vision and graft thickness in deep anterior lamellar and penetrating corneal allografts. *Am J Ophthalmol* 2007; **143**(2): 228–235.

10 Kubaloglu A, Sari ES, Unal M, Koytak A, Kurnaz E, Cinar Y *et al.* Long-term results of deep anterior lamellar keratoplasty for the treatment of keratoconus. *Am J Ophthalmol* 2011; **151**(5): 760–767.

11 Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty a report by the american academy of ophthalmology. *Ophthalmology* 2011; **118**(1): 209–218.

12 Borderie VM, Boelle PY, Touzeau O, Allouch C, Boutboul S, Laroche L. Predicted long-term outcome of corneal transplantation. *Ophthalmology* 2009; **116**(12): 2354–2360.

13 Bahar I, Kaiserman I, McAllum P, Rootman D. Femtosecond laser-assisted penetrating keratoplasty: stability evaluation of different wound configurations. *Cornea* 2008; **27**(2): 209–211.

14 Mosca L, Fasciani R, Tamburelli C, Buzzonetti L, Guccione L, Mandara E *et al.* Femtosecond laser-assisted lamellar keratoplasty: early results. *Cornea* 2008; **27**(6): 668–672.

15 Por YM, Cheng JY, Parthasarathy A, Mehta JS, Tan DT. Outcomes of femtosecond laser-assisted penetrating keratoplasty. *Am J Ophthalmol* 2008; **145**(5): 772–774.

16 Shehadeh-Mashor R, Chan C, Yeung SN, Lichtinger A, Amiran M, Rootman DS. Long-term outcomes of femtosecond laser-assisted mushroom configuration deep anterior lamellar keratoplasty. *Cornea* 2013; **32**(4): 390–395.

17 Buzzonetti L, Petrocelli G, Valente P. Femtosecond laser and big-bubble deep anterior lamellar keratoplasty: a new chance. *J Ophthalmol* 2012; **2012**: 264590.

18 Lee WB, Jacobs DS, Musch DC, Kaufman SC, Reinhart WJ, Shtein RM. Descemet's stripping endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. *Ophthalmology* 2009; **116**(9): 1818–1830.

19 Price MO, Baig KM, Brubaker JW, Price Jr FW. Randomized, prospective comparison of precut vs surgeon-dissected grafts for descemet stripping automated endothelial keratoplasty. *Am J Ophthalmol* 2008; **146**(1): 36–41.

20 Anshu A, Price MO, Tan DT, Price Jr FW. Endothelial keratoplasty: a revolution in evolution. *Surv Ophthalmol* 2012; **57**(3): 236–252.

21 Phillips PM, Phillips LJ, Much JW, Maloney C. Descemet stripping endothelial keratoplasty: six-month results of the first 100 consecutive surgeries performed solo by a surgeon using 1 technique with 100% follow-up. *Cornea* 2012; **31**(12): 1361–1364.

22 Price MO, Fairchild KM, Price DA, Price Jr FW. Descemet's stripping endothelial keratoplasty five-year graft survival and endothelial cell loss. *Ophthalmology* 2011; **118**(4): 725–729.

23 Allan BD, Terry MA, Price Jr FW, Price MO, Griffin NB, Claesson M. Corneal transplant rejection rate and severity after endothelial keratoplasty. *Cornea* 2007; **26**(9): 1039–1042.

24 Neff KD, Biber JM, Holland EJ. Comparison of central corneal graft thickness to visual acuity outcomes in endothelial keratoplasty. *Cornea* 2011; **30**(4): 388–391.

25 Shinton AJ, Tsatsos M, Konstantopoulos A, Goverdhan S, Elsahn AF, Anderson DF *et al.* Impact of graft thickness on visual acuity after Descemet's stripping endothelial keratoplasty. *Br J Ophthalmol* 2012; **96**(2): 246–249.

26 Price MO, Price Jr FW, Stoeger C, Soper M, Locke GD, Bavuso T. Central thickness variation in precut DSAEK donor grafts. *J Cataract Refract Surg* 2008; **34**(9): 1423–1424.

27 Mukherjee A, Voyatzis G, Rajan MS. Reply to 'Descemet stripping automated endothelial keratoplasty: effect of intraoperative lenticule thickness on visual outcome and endothelial cell density'. *Cornea* 2013; **32**(1): 108–109.

28 Busin M, Patel AK, Scorcia V, Ponzin D. Microkeratome-assisted preparation of ultrathin grafts for descemet stripping automated endothelial keratoplasty. *Invest Ophthalmol Vis Sci* 2012; **53**(1): 521–524.

29 Thomas PB, Mukherjee AN, O'Donovan D, Rajan MS. Preconditioned donor corneal thickness for microthin endothelial keratoplasty. *Cornea* 2013; **32**(7): e173–e178.

30 Melles GR, Lander F, Rietveld FJ. Transplantation of Descemet's membrane carrying viable endothelium through a small scleral incision. *Cornea* 2002; **21**(4): 415–418.

31 Melles GR, Ong TS, Ververs B, van der Wees J. Descemet membrane endothelial keratoplasty (DMEK). *Cornea* 2006; **25**(8): 987–990.

32 Price MO, Price Jr FW. Descemet's membrane endothelial keratoplasty surgery: update on the evidence and hurdles to acceptance. *Curr Opin Ophthalmol* 2013; **24**(4): 329–335.

33 Tourtas T, Laaser K, Bachmann BO, Cursiefen C, Kruse FE. Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty. *Am J Ophthalmol* 2012; **153**(6): 1082–1090.

34 Anshu A, Price MO, Price Jr FW. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. *Ophthalmology* 2012; **119**(3): 536–540.

35 Price MO, Price FW. Descemet's stripping endothelial keratoplasty. *Curr Opin Ophthalmol* 2007; **18**(4): 290–294.

36 Mehta JS, Chua J, Poh R, Beuerman RW, Tan D. Primary graft failure after Descemet-stripping automated endothelial keratoplasty: clinico-pathological study. *Cornea* 2008; **27**(6): 722–726.

37 Koizumi N, Sakamoto Y, Okumura N, Okahara N, Tsuchiya H, Torii R *et al.* Cultivated corneal endothelial cell sheet transplantation in a primate model. *Invest Ophthalmol Vis Sci* 2007; **48**(10): 4519–4526.

38 Joyce NC. Proliferative capacity of corneal endothelial cells. *Exp Eye Res* 2012; **95**(1): 16–23.

39 Okumura N, Koizumi N, Ueno M, Sakamoto Y, Takahashi H, Tsuchiya H *et al.* ROCK inhibitor converts corneal endothelial cells into a phenotype capable of regenerating *in vivo* endothelial tissue. *Am J Pathol* 2012; **181**(1): 268–277.

40 Lee JG, Kay EP. Two populations of p27 use differential kinetics to phosphorylate Ser-10 and Thr-187 via phosphatidylinositol 3-Kinase in response to fibroblast growth factor-2 stimulation. *J Biol Chem* 2007; **282**(9): 6444–6454.

41 Koizumi N, Okumura N, Kinoshita S. Development of new therapeutic modalities for corneal endothelial disease focused on the proliferation of corneal endothelial cells using animal models. *Exp Eye Res* 2012; **95**(1): 60–67.

42 Peh GS, Beuerman RW, Colman A, Tan DT, Mehta JS. Human corneal endothelial cell expansion for corneal endothelium transplantation: an overview. *Transplantation* 2011; **91**(8): 811–819.

43 Peh GS, Lee MX, Wu FY, Toh KP, Balehosur D, Mehta JS. Optimization of human corneal endothelial cells for culture: the removal of corneal stromal fibroblast contamination using magnetic cell separation. *Int J Biomater* 2012; **2012**: 601302.

44 Levis HJ, Peh GS, Toh KP, Poh R, Shortt AJ, Drake RA *et al.* Plastic compressed collagen as a novel carrier for expanded human corneal endothelial cells for transplantation. *PLoS One* 2012; **7**(11): e50993.