Corneal stem cells in the eye clinic

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Introduction or background: Corneal opacity is a common cause of blindness. The majority of cases result from ulceration and scarring following infection or trauma, but in a proportion corneal epithelial stem cell (SC) deficiency leads to an inability to maintain a healthy corneal surface.

Sources of data: This review includes systematic reviews and individual case series of treatments for corneal epithelial SC deficiency.

Areas of agreement: Two techniques such as transplantation of large segments of cornea from a healthy eye and ex vivo expansion of corneal SCs in the laboratory were compared. Both have merits and their clinical outcomes are similar. The smaller biopsy in the cell expansion approach has less risk for the donor eye, which is a significant advantage.

Areas of controversy: Treatment algorithms for different aetiologies of SC failure are evolving. The proportion of true corneal epithelial SCs in ex vivo culture is unclear and it is unknown whether these cells survive long term.

Growing points: In this study, the optimum method of cell culture and transplantation is being intensively investigated.

Areas timely for developing research: Development of tissues using multiple cell types, genetic modification to treat hereditary corneal disorders and development of cell therapy for other eye diseases are future possibilities.

Keywords: somatic stem cell biology/stem cell culture/transplantation/cornea/limbal stem cell deficiency

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Background

Why is visual loss important and how does it affect the world, the NHS and society?

Visual loss is universally feared. A recently published survey ‘Eye on Eyesight’ found that, in Americans between the age of 50 and 64 years, the fear of losing sight was nearly double that of getting heart disease (63 vs. 37%). This age group has the highest risk for heart disease as well as the most common conditions that can cause visual disability such as macular degeneration, glaucoma and diabetic retinopathy. The survey also showed that 79% of respondents said that, apart from their own death or the death of a loved one, the loss of eyesight was the ‘worst thing that could happen to me’, clearly positioning vision as one of the most important elements of one’s life, if not the most important.

In 1997, the WHO estimated that worldwide there were up to 38 million blind people and 110 million with low vision. Importantly, it was estimated that at least two-thirds of this blindness was avoidable (treatable or preventable) and that interventions to prevent or cure blindness were extremely cost-effective. In response to this global burden of blindness, the WHO launched the ‘VISION 2020: The Right to Sight’ initiative (http://www.vision2020.org) with the aim of eliminating avoidable blindness by the year 2020.

There are considerable economic consequences of visual impairment. These include the direct costs of eye care health programmes and the secondary costs such as labour productivity loss, the costs of carers and equipment and, finally, the social welfare losses that result from premature death. The latter is usually calculated as disability-adjusted life years (DALYs), an estimate of the number of years lost due to premature mortality or morbidity resulting from a particular medical state. Using this methodology, visual impairment ranks as the seventh leading cause of disability worldwide, after perinatal conditions, lower respiratory infection, cardiovascular and cerebrovascular diseases and HIV/AIDS. The direct and indirect costs of visual impairment and treating eye disease in the UK for 2008 was equivalent to 0.45% of GDP (USD 1.2 billion).

What are the main causes of blindness?

The latest available global data on the causes of blindness are based on 2004 estimates (Fig. 1). The leading causes of blindness are cataract (39% of cases), uncorrected refractive error (18%), glaucoma (10%) and age-related macular degeneration (7%). Corneal scarring and opacity was the joint fifth commonest cause of blindness, accounting...
for 4.3% of cases. However, this figure does not include corneal scarring associated with trachoma, which accounts for an additional 3% of world blindness.

**Causes of corneal scarring and opacity**

The normal cornea is completely transparent (Fig. 2A). This is a function of the highly specialized structure of the cornea, which is composed of three main layers: the surface epithelium, central stroma and the inner endothelium. Corneal opacity can result from damage to any or all of the corneal layers (Fig. 2B). Common causes of corneal scarring include acute trauma, infection, chronic inflammation and exposure. Specific conditions are summarized in Table 1.
Treatment of corneal scarring and opacity

Eduard Zirm performed the first corneal transplant in 1905, which makes it one of the earliest types of tissue transplantation. For full thickness corneal transplantation (penetrating keratoplasty, PK), a 7.5 mm diameter disc of all layers of the centre of the cornea is excised and replaced with a similar disc of donor tissue that is secured with sutures. A PK is very effective in the avascular cornea, but allograft rejection, usually directed against the corneal endothelium, can still occur even when the cornea is avascular. The risk of allograft rejection is further increased if there has been previous surgery or if the cornea is vascularized. As an alternative to PK, there has been a rapid development in the last 10 years of lamellar techniques of corneal transplantation that only replace the corneal layers affected by disease or scarring. Replacement of diseased endothelium is achieved by posterior lamellar endothelial keratoplasty and corneal scarring limited to the stroma can be treated by anterior lamellar keratoplasty in which the endothelium is left undisturbed. These techniques are effective at treating corneal opacity from various causes, but they cannot treat corneal disease due to failure of the epithelial layer of the ocular surface from corneal epithelial stem cell (SC) deficiency (LSCD). Management of LSCD requires a separate approach.

Table 1 The most common causes of corneal opacity. Multiple risk factors may apply.

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Physical/traumatic</th>
<th>Inflammatory</th>
<th>Corneal exposure</th>
<th>Genetic</th>
<th>Nutritional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Bacterial keratitis</td>
<td>Penetrating</td>
<td>Alkali injury</td>
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<td></td>
<td>Herpes simplex</td>
<td>corneal injury</td>
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<td>keratitis</td>
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<td>Measles</td>
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<td>Onchocerciasis</td>
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<tr>
<td>Chronic</td>
<td>Herpes simplex</td>
<td>Trachoma</td>
<td>Fuchs</td>
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<td>Vitamin A</td>
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<td></td>
<td>related chronic/</td>
<td></td>
<td>endothelial</td>
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<td></td>
<td>recurrent</td>
<td></td>
<td>dystrophy</td>
<td></td>
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<td></td>
<td>inflammation</td>
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<td></td>
<td>Pseudophakic</td>
<td>SJS</td>
<td>Aniridia</td>
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<td></td>
<td>bulous</td>
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<td>keratopathy</td>
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<tr>
<td></td>
<td>Acid injury</td>
<td>Facial nerve</td>
<td>Vitamin A</td>
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<td></td>
<td></td>
<td>palsy</td>
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<td>Peters</td>
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<td>anomaly</td>
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**Limbal SCs and the effects of deficiency**

The corneal epithelium is the outermost corneal layer and is exposed to the external environment. Like all stratified squamous epithelia, it undergoes continuous cell turnover. The shedding of cells from the surface into the tear pool is balanced by the outward migration of basal cells into the stratified layers, while the basal cells are in turn replaced by cells from the periphery that move towards the centre of the cornea. In stratified epithelia such as skin and gut, SCs are scattered throughout the epithelial layer and its appendages. In contrast, the corneal epithelial SCs are thought to be concentrated in the basal epithelial layer at the peripheral zone of the cornea. There is only limited evidence that corneal cells with high regenerative potential can be located in the centre of the cornea. This peripheral zone of the cornea is called the limbus (highlighted in Fig. 2A) and the basal cells in this region are referred to as either corneal epithelial SC or more correctly as limbal epithelial SC. The limbus is adapted to form an environmental niche with specialized blood vessels and supporting stroma. These potentially opaque structures are therefore away from the optical zone of the cornea.

Destruction of limbal SC or their niche results in a characteristic clinical picture of LSCD. This can follow an acute direct damage to the limbal SC resulting in cell death as is seen after chemical or thermal burns. Alternatively, it results from chronic inflammation and physical insult resulting in effective ‘burn-out’ of the homeostatic system. The loss of the normal corneal epithelial phenotype is often associated with ulceration and scarring of the corneal surface and underlying stroma, corneal thinning and an irregular corneal surface. As a compensatory mechanism, the conjunctival epithelium from peripheral to the cornea (Fig. 2A) grows centrally over the surface of the cornea. The clinical signs of this conjunctival overgrowth are marked epithelial haze, superficial vascularization, epithelial instability and epithelial surface irregularity. The diagnosis can be confirmed by impression cytology looking for the expression of cytokeratins characteristic of cells of a conjunctival origin. The leading causes of LSCD in the UK are chemical/thermal injury, Stevens Johnson syndrome (SJS), aniridia and ocular cicatricial pemphigoid (OCP). The combined incidence of these conditions is 1:25 000 and using a conservative estimate that 10% of these patients develop LSCD, this amounts to 240 new cases of per year in the UK alone. The severity can vary from mild vascularization and surface irregularity, for example due to contact lens overwear, to severe total corneal ulceration.
Sources of data

This review used an evidence-based approach. A literature search was performed to identify review articles and original studies describing the process and outcomes of limbal SC transplantation. Treatments could be classified into two groups. The first was the group of direct tissue transfer where large segments of corneal limbus are transplanted from a healthy eye to an SC-deficient cornea (called direct tissue transfer). The second group used \textit{ex vivo} laboratory-based expansion of limbal SC to produce a corneal epithelial sheet for transplantation back onto the SC-deficient cornea. Table 2 lists the information sources that were used arranged according to the strength of evidence they provide. The lack of high-quality objective data in the form of randomized controlled trials or meta-analyses is an inherent problem with surgical procedures as they are less suited to this study design than other medical interventions. This is especially so for new surgical procedures.

Areas of agreement

Management/treatment of patients with limbal SC deficiency

Ocular surface disease that results from LSCD poses a difficult management problem. From the patient’s perspective, the eye has little or
no vision, it is often cosmetically unsatisfactory, and it may be uncomfortable or painful. The clinical consequences are recurrent or persistent ulceration of the corneal surface, which places the cornea at risk of thinning, vascularization or infection. However, in a proportion of cases, the eye may be otherwise healthy with good visual potential. Because the problem is often bilateral, the patient is effectively blind and in pain. An effective treatment would offer a significant gain in quality of life.23–25

Conservative options

Conservative management options for patients with LSCD include intensive lubrication with non-preserved artificial tear drops or the use of a contact lens to protect the corneal surface and provide pain relief. The use of 10–20% autologous serum eye drops also reduces inflammation and promotes epithelial healing.26–28

Surgical options for total limbal SC deficiency

In patients with severe ocular disease such as SJS, OCP or following severe chemical/thermal burns, a standard PK is unlikely to survive. This is because secondary changes such as dry eye, inflammation or exposure create a hostile environment that destroys the transplanted tissue. Ocular surface reconstruction (OSR) describes a three-step approach to restoring a normal ocular surface:

(i) Correct tear film and lid abnormalities: This may include occlusion of the lacrimal punctae to prevent tear drainage via the lacrimal drainage system. Abnormalities of the eyelids, such as incomplete lid closure (lagophthalmos), ingrowing eyelashes (trichiasis) or posterior rotation of the eyelid margin (entropion) should be corrected.

(ii) Remove the abnormal epithelium and associated scar tissue: Subepithelial fibrosis is a common accompaniment of limbal epithelial SC failure. This tissue must be removed prior to SC transfer. There is often a tissue plane beneath this scar tissue, which can be stripped with relative ease. If the cornea is thinned or scarred, donor corneal tissue or human amniotic membrane may be used.

(iii) Transplant corneal limbal epithelial SC to re-establish an intact and transparent epithelium: When there is total limbal epithelial SC failure autologous or allogeneic limbal SC can be transplanted. Originally, this was performed by direct transplantation of whole segments of donor limbus onto the recipient limbus (Fig. 2A and B). A more recent alternative is to culture in vitro cells isolated from a small limbal biopsy to produce an epithelial sheet for transplantation (Fig. 2C).
Direct transfer of whole segments of limbus

In 1986, Kenyon and Tseng reported that a corneal epithelial phenotype could be restored by direct transfer of healthy limbal tissue onto the SC deficient cornea. This method is still used and has the advantages that it is cheaper than \textit{in vitro} techniques, it is logistically easier to arrange, and the transplanted epithelial SC are contained in their natural environment (niche). The source of the limbal tissue can be from a deceased donor, autologous tissue from the fellow healthy eye or limbal tissue donated by a living relative. The differences between these techniques are illustrated in Figure 3A and B.

Ex vivo \textit{expansion and transplantation of cultured limbal SC}

The laboratory-based technique of cultured limbal epithelial transplantation (CLET) was one of the first examples in regenerative medicine of
a cell therapy. In contrast to limbal tissue transfer, the cells used for CLET are obtained from a relatively small biopsy of limbal tissue. This is transferred to a dedicated tissue culture facility where the limbal SCs are harvested and grown to form a confluent epithelial sheet. Various materials (e.g. fibrin or amniotic membrane) may be used as a cell substrate to facilitate transfer of the cells from culture back onto the prepared surface of the recipient cornea (Fig. 2C). Since 1997 there have been over 20 peer-reviewed publications describing its use in over 200 patients. Although it is commonly referred to as SC therapy, the sheet of cultured cells is not composed purely of limbal SC, but is a mixture of SC and more differentiated daughter cells. A closely related therapy, \textit{ex vivo} cultured autologous oral mucosal epithelial transplantation (COMET), has also been used to treat LSCD.

The potential advantages of CLET are that the size of the biopsy is substantially less than that is required for the direct limbal transplantation (although more than one biopsy may be required to obtain a successful cell culture) and this minimizes the risk of inducing surface failure from LSCD in the donor eye. The smaller size of the biopsy also means that a normal region of the contralateral eye can still be used as a source of tissue when there is partial SC failure. CLET may also have a reduced risk of allograft rejection compared with direct tissue transfer because antigen-presenting macrophages do not survive the process of \textit{ex vivo} culture. It is also technically possible to cryopreserve excess \textit{ex vivo} cultured cells for prolonged period, which would provide a source of additional cells for transplantation should the need arise.

\textbf{Outcomes of limbal transplantation}

\textbf{Problems comparing outcomes}

The classification of the various tissue transfer techniques is used to define outcomes. The potential outcome measures include the time to epithelial healing, stability of epithelium, pattern of fluorescein dye staining, epithelial neovascularization and visual acuity, but there is no universally accepted system. For the purpose of this review, studies were examined for data on:

(i) Improvement in ocular surface transparency and stability.

(ii) Visual acuity.

(iii) Quality-of-life assessment and subjective symptoms.

Despite these, the results must be interpreted carefully because of heterogeneity in the diseases treated, differences in culture methods and carriers substrates, variation in follow-up, and the fact that some
patients underwent subsequent surgical procedures such as PK, cataract surgery or repeated CLET.

**Outcomes of direct tissue transfer vs. CLET**

Data on improvement in corneal surface integrity and visual acuity were extracted from systematic reviews.\(^9,60–62\) These reviews incorporated data from all studies available at the time of their publication. In addition, two recent important studies by Liang \(^{63}\) and Biber \(^{64}\) have been assimilated and the data are summarized in Table 3.

### Results with transplantation of ex vivo cultured oral mucosal epithelium

Cells obtained from heterotopic sites have been evaluated as an alternative to limbal cell transfer. Cultured oral mucosal epithelial transplantation (COMET) has several potential advantages.\(^{51,55,57,65–71}\) There is a plentiful supply of tissue and patients may be happier for a biopsy to be taken from the mouth rather than risk damaging their unaffected eye. Importantly, there is no risk of immune-mediated rejection, and, in the absence of autoimmune disease, immunosuppression is not required. Disadvantages of COMET are a high rate of recurrence of corneal neovascularization and epithelial haze. Published outcomes for COMET show a stable corneal surface is achieved in up to 100% of eyes at 1 year,\(^{69}\) 100% at 14 months,\(^{57}\) 67% at 20 months\(^{55}\) and 92% at 4 years.\(^{70}\) Visual acuity was better than pre-treatment levels in 90% of eyes at 1 year,\(^{69}\) 100% at 14 months,\(^{57}\) 67% at 20 months\(^{55}\) and 53% remained improved for 4 years following surgery.\(^{70}\)

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**Table 3** Results of direct tissue transfer and ex-vivo cell expansion techniques.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Type of graft</th>
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<tbody>
<tr>
<td></td>
<td>CLAU</td>
</tr>
<tr>
<td>Corneal surface improvement</td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>98.6%</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>93.4%</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>80%</td>
</tr>
<tr>
<td>Improved visual acuity</td>
<td>96%</td>
</tr>
</tbody>
</table>

CLAU, conjunctival-limbal autologous transplant; KLAL, keratolimbal allogeneic transplant; Ir-CLAL, living-related conjunctival-limbal allogeneic transplant; CLET, cultured limbal epithelial transplant.

\(^{a}\)This value related to eyes that underwent combined lrCLAU and KLAL and had improvement in their ocular surface (33.3%) or a stable ocular surface (54.2%) relative to their pre-treatment condition.\(^{64}\)

\(^{b}\)Liang et al.\(^{63}\)
Regulatory considerations governing the *ex vivo* culture of limbal SC for clinical purposes

The technology of culturing cells for human transplantation is tightly regulated in the EU under the auspices of the European Medicines Agency. Advanced Therapy Medicinal Products (ATMPs), including somatic cell therapy, gene therapy and tissue engineering, must be manufactured in Good Manufacturing Practice compliant facilities operating a robust quality management system. In the UK, such facilities are inspected and licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) through manufacturing licenses for ‘Specials’ and/or Investigational Medicinal Products. If the manufacturing facility procures human tissue as a starting point for such processes, a license from the UK Human Tissue Authority is also required in accordance with the EU Tissues and Cells Directive. The purpose of this legislative and regulatory framework is to ensure that ATMP materials are obtained, processed and stored in an ethically and legally approved manner to minimize risk and optimize potential therapy efficacy. In April 2007, the National Institute of Clinical excellence (NICE) issued guidance on tissue-cultured limbal SC allograft transplantation and stated that efficacy and safety data were not adequate for this procedure to be used without special arrangements for consent and for audit of research.

Areas of controversy

*Is ex vivo expansion of autologous cells better than conventional limbal SC transplantation?*

Evidence indicates that direct tissue transfer and CLET have comparable outcomes (Table 3). If this is true, then CLET would be the procedure of choice for an autologous or living-related donor procedure because of the small biopsy that is required. CLET biopsies are a fraction of the size of that in direct tissue transfer, which minimizes the risk to the donor eye. However, CLET requires the support of a dedicated laboratory and staff, which makes the treatment much more expensive than direct tissue transfer. Cost-effectiveness should therefore be included in the design of any controlled clinical trial comparing these techniques.

Emerging treatment algorithm

Available data show that for patients with long-standing unilateral alkali injuries, the procedure of choice is autologous CLET.72 Beyond this, the evidence on which procedure to use and in which disease entity is unclear. In the remaining cases of unilateral LSCD, which are mostly acid, thermal or trauma related, CLAU or autologous CLET...
should be considered. In bilateral disease, there is controversy as to whether \textit{ex vivo} expanded cells (i.e. allogeneic CLET or COMET) offer an advantage over direct tissue transfer techniques (lr-CLAU, KLAL). Until recently, long-term outcome data for KLAL was universally poor (Table 3) but a more potent immunosuppressive regime combining tacrolimus and mycophenolate with a short course of oral steroids KLAL graft survival can be significantly prolonged.\textsuperscript{63,64} Another novel way of improving outcomes of these allogeneic direct tissue transfer techniques is to combine lr-CLAL and KLAL (the Cincinnati Procedure). This gives superior outcomes to KLAL outcomes alone.\textsuperscript{64} COMET offers autologous tissue with plentiful supply, but is associated with high postoperative rates of recurrent neovascularization and epithelial haze. Allogeneic CLET provides the correct cell phenotype but with the need for systemic immunosuppression. A lack of data, particularly on the long-term outcomes of allogeneic CLET, make it impossible to draw conclusions regarding which is superior.

\textbf{What is the evidence for the presence of SC within \textit{ex vivo} CLET grafts?}

Although there is not a definitive marker for limbal SC, there is strong evidence that CLET grafts contain SC, but that they are mixed with more differentiated epithelial. It is estimated that between 2 and 9\% of cells in \textit{ex vivo} expanded limbal epithelial cultures are SC.\textsuperscript{45,73} This is similar to the estimate that SC comprise 9\% of total limbal epithelial cells.\textsuperscript{74–76}

\textbf{What is the evidence that transplanted cells survive}

Investigation of cell survival requires direct sampling of the corneal epithelial surface. Polymerase chain reaction genotyping has been used to detect transplanted allogeneic cells following both direct tissue transfer and CLET allografts. This suggests that, in the majority of patients, donor cells may persist for 7–9 months, but they are then replaced by host cells. Cytokeratin profiling and \textit{in vivo} confocal microscopy shows that a corneal epithelial phenotype is present at both 7 months\textsuperscript{37} and 10 months.\textsuperscript{31} This confirms the potential of this method to restore a corneal phenotype in limbal SC-deficient corneas although transplanted allogeneic cells probably do not survive long term.

\textbf{Are allogeneic cells the subject of immune rejection}

Histological analysis of failed allografts shows evidence of immune-mediated rejection of allogeneic cells that may be enhanced by
inflammation from chronic ocular disease. Systemic immunosuppression has been used to reduce the risk of allograft rejection in both CLET and KLAL. Despite continuous oral administration of ciclosporin A (CSA) for several years, the long-term success rate of KLAL is poor, and there is no evidence that oral CSA improves outcomes. Similarly, there is as yet no evidence that tissue-matching is effective. Two studies have shown that a more aggressive immunosuppressive regime of tacrolimus and mycophenolate along with a short (up to 3 months) course of oral steroid can substantially improve the outcome of direct tissue allografts.

What is the mechanism of action of CLET

It is thought that either the limbal SC in the cultured LEC sheet repopulate the recipient’s limbal SC niche (re-integration hypothesis) or that they stimulate for the patient’s own endogenous limbal SC population to regenerate (biological bandage hypothesis).

Growing points

The treatment of corneal LSCD has become focused on the CLET approach. The optimum method of graft culture has yet to be determined and xenobiotic-free culture processes are being investigated. The long-term results of autografts and allografts will inform future treatment algorithms and techniques. The methods of assessing success are currently poorly defined and better objective methods are required to compare outcomes. Techniques for culturing conjunctival cells are under development and this will offer a further advance for OSR. Bioengineered materials for culture substrates are under development. These will remove the variability of current biological substrates such as human amniotic membrane.

Areas timely for developing research

In the future, it is possible that cell therapy will become a routine tool for reconstructing ageing or damaged tissue. At present, individual cell types are transplanted the use of complex substrates with multiple cell types could enable the replacement multiple tissue layers in one procedure. The development of a three-dimensional scaffolds could allow more complex tissue and organ generation. It is likely that alternative autologous cell sources such as nasal mucosa or hair follicle SC could be used for corneal reconstruction. In the long term, less differentiated
cells such as tooth pulp or embryonic SC have immense potential. Finally, it may be possible to modulate the disease process by the in vitro manipulation of cells with gene therapy, RNA inhibition or drugs to either correct genetic defects (e.g. in aniridia) or to optimize their function once transplanted.81

Glossary

SC, Stem cell; PK, Penetrating keratoplasty or corneal transplant; Limbal SC, The cells located at the corneal limbus that are responsible for maintaining and regenerating a healthy corneal epithelium; Corneal limbus, The zone at the periphery of the cornea where the transparent corneal tissue meets the opaque scleral tissue. This is the location of limbal stem cells; LSCD, Limbal stem cell deficiency. The state where limbal stem cells are destroyed by disease resulting in ulceration and scarring of the cornea.

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