



Ocular Surface Reconstruction with BrightMEM™ Corneal Allografts

A foundation for Durable Epithelial Regeneration

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The corneal epithelium has many essential roles, including serving as a barrier to external trauma, germs, toxins, and environmental threats and providing a smooth refractive surface to facilitate vision. Like all epithelial layers in the body, there is constant turnover of epithelium, which is dependent upon proliferative cells in the limbus and basal layers of the epithelium. These cells mature and differentiate, regenerating the normal corneal epithelium throughout life (1-3). When the protective epithelial layer is disrupted, the eye becomes susceptible to infection, degradation of underlying corneal tissue (stromal ulceration), perforation, scarring, and significant vision loss (4-6). Persistent corneal epithelial defects (PCEDs) and limbal stem cell deficiency (LSCD) are two challenging diseases where there is pathologic healing of the corneal epithelium. While there are medical and surgical therapies to promote healing of damaged corneal epithelium in these cases, therapies that provide long-term resolution of these diseases remain limited.

Background

PERSISTENT CORNEAL EPITHELIAL DEFECT

A persistent corneal epithelial defect (PCED) occurs when there is a failure of reepithelialization after a corneal injury. According to recent estimates, there are approximately 97,000 cases of PCED a year in the United States (7). Though there is no consensus definition or specific time frame for when delayed healing is considered pathologic (5,6), any prolonged healing time for corneal epithelial defects increases the risk of stromal melting, vision-reducing haze or scarring, and infection. Damage to the epithelial basement membrane, the substrate that supports healthy epithelial cells, can lead to recurrent corneal erosions (8). Therefore, healing any corneal epithelial defect as quickly as possible is essential to prevent long-term complications and reduced vision.

Delayed corneal epithelial wound healing may be caused by different mechanisms, such as active microbial infection, decreased corneal innervation (neurotrophic cornea), underlying limbal stem cell deficiency (LSCD), surgical/mechanical/thermal trauma, and chronic expo-sure with resultant tear evaporation and desiccation (1).

Normal corneal epithelial healing is driven by the orchestrated efforts of multiple biologic pathways, including cell proliferation and migration (9), cell-to-cell signaling, and extracellular matrix remodeling and the interplay of numerous growth factors and cytokines (1,3).

Pathophysiologic processes that become activated in the setting of nonhealing corneal epithelial defects or abnormal epithelial cell turnover (as in LSCD) can result in disordered extracellular matrix deposition and proliferation of abnormal cells (e.g., myofibroblasts) with aberrant healing. This can cause the cornea to become opacified, resulting in reduced visual acuity (1,3).

Effective treatment of abnormal (LSCD) or nonhealing corneal epithelium (PCED) across its various etiologies requires a multifactorial approach including both medical and surgical interventions. Patients with these conditions experience significant clinical burden and, despite treatment, may suffer sight-threatening complications. Patients suffer significant symptoms including pain, redness, and photophobia and often develop complications including corneal neovascularization, infection, opacification, and subsequent vision loss (1,10). Serious complications, including corneal ulcers, corneal perforation, irreversible scarring, melting, and lifelong recurrent corneal erosions impact a significant number of patients (1,11).

LIMBAL STEM CELL DEFICIENCY

Homeostasis and transparency of the corneal epithelial surface are maintained by continuous regeneration of the corneal epithelium throughout a patient's life. Stem cells located in the basal layer of limbal epithelium (limbal stem cells) proliferate, migrate, and differentiate to become mature corneal epithelial cells (12). Dysfunction (LSCD) or loss of these cells (e.g., from trauma, chemical, or thermal injury) leads to the vision-threatening sequelae listed previously (13). LSCD is a challenging disease to diagnose, due to the frequent presence of comorbid diseases (e.g., eyelid abnormalities, compromised corneal innervation, dry eyes, ocular surface inflammation, etc.) and the overlap in clinical appearance with more common diseases (e.g., pterygium, phlyctenulosis, etc.). This often leads to delayed treatment.

According to orphanet.net the prevalence of LSCD in the U.S. is around 165,000 cases per year (14). A diagnosis of LSCD is mostly made clinically, based on slit lamp examination with the presence of whirl-like keratopathy, late fluorescein staining, corneal conjunctivalization, and/or superficial neovascularization. However, this method is highly subjective, with significant limitations, as the signs of an abnormal epithelium can be subtle and are not specific to LSCD. Diagnosis is aided by a combination of impression cytology, in vivo laser scanning confocal microscopy, and anterior segment optical coherence tomography. (15)

LSCD can be congenital in patients with aniridia, keratitis associated with multiple endocrine deficiency, dyskeratosis congenita, and epidermal dysplasia. Common causes of acquired LSCD include chemical and thermal burns, ocular surgeries involving the limbal region, contact lens overwear, and chronic ocular surface inflammatory diseases (12,13). Immunologic diseases such as Stevens-Johnson syndrome and mucous membrane pemphigoid are also known to lead to LSCD. All of these conditions may result in direct damage to the limbal stem cells (LSC) as well as the stem cell microenvironment/niche. (12,13)

Importance of the Limbal Niche

A healthy population of LSCs is critical for long-term maintenance of the corneal epithelium. The limbal niche is the microenvironment found in the limbus that surrounds the LSCs. The limbal niche is extremely complex and includes the extracellular matrix of the limbus and its microstructure, as well as the nerves, blood vessels, melanocytes, and mesenchymal stem cells found in the limbus. This niche microenvironment is critical for maintaining the LSCs' survival and proliferative potential under physiologic conditions (16,17). Extracellular signals from the microenvironment drive the normal function and maintenance of LSCs (18). Without the support of a niche-like microenvironment, LSCs on the ocular surface eventually terminally differentiate or die over time. This is supported by the observation that, following transplantation of cultured LSCs onto the ocular surface, poor long-term survival of the transplanted LSCs has been observed. Even in the absence of rejection, transplanted cultured LSCs on their own have been shown to have limited survival beyond nine months when tracked (19,20). This is different from results following surgeries where both LSCs and a limbal niche are transplanted (e.g., keratolimbal allograft or KLAL). The limbal niche is a critical driver of LSC proliferation and corneal epithelial regeneration long term.

Current Treatment Options

To treat severe ocular surface disorders such as PCED and LSCD, corneal epithelial cells must have an environment that supports their survival, maturation, and multiplication. Current therapeutic approaches have significant limitations and frequently fail to achieve long-term resolution of the disease. Consequently, recurrence of epithelial pathology is common in these disease states.

TREATMENT FOR PCED

The goal of treatment in PCEDs is to both regenerate the corneal epithelium and maintain that epithelium long term. To achieve this, favorable conditions must be provided for the corneal epithelial cells to proliferate, migrate, and establish a self-sustaining corneal epithelial layer (1).

Conventional medical therapies for PCEDs employ numerous strategies to achieve these goals, but most are not effective, long term, in correcting all the multifactorial pathophysiologic abnormalities that impair corneal epithelial healing (21).

While there is no universally agreed-upon treatment algorithm, the following interventions are commonly employed in PCEDs:

- **Ocular surface lubrication.** Ocular lubricants (tears, gels, and ointments) and punctal plugs serve to increase tear volume. Increased lubrication decreases mechanical stress/friction on the epithelium and reduces desiccation of the epithelial cells.
- **Autologous serum.** Autologous serum is a more advanced ocular lubricant that better mimics the protein and lipid composition in natural tears and provides growth factors to

help corneal epithelial cells proliferate in addition to lubrication. As a result, autologous serum is often superior to over-the-counter ocular lubricants.

- **Contact lenses.** Soft bandage contact lenses can be applied to the ocular surface to reduce mechanical trauma from the eyelids blinking. Scleral contact lenses are particularly helpful by keeping a “reservoir” of tears on the cornea to bathe the epithelium (22).
- **Amniotic membrane.** Amniotic membranes provide a temporary wound covering and likely release growth factors to help cells proliferate. Because amniotic membranes are commonly short-lived and dissolve in 7-20 days, they may need to be reapplied numerous times.
- **Tarsorrhaphy.** Partially or completely fusing the lids closed can reduce the surface area for tear evaporation and limit the mechanical trauma from eyelids blinking, but they also significantly compromise vision.
- **Conjunctival flap.** Conjunctival flaps create a protective, vascularized mucosal surface for the cornea using the patient’s own conjunctiva. This reduces the likelihood of stromal melting, but corneal transparency and vision are usually severely compromised.
- **Limbal stem cell grafts.** LSC grafts provide additional stem cells to regenerate the corneal epithelium, but require systemic immunosuppression when using donor cells.
- **Penetrating keratoplasty.** Penetrating keratoplasty is generally performed only when all other measures have failed and corneal perforation is imminent. Although it can restore the corneal architecture in cases where there is melting, scarring, or perforation, PCEDs can easily recur in the graft unless the underlying disease is addressed.

TREATMENT FOR LSCD

Treatment of LSCD requires reestablishing a functional population of LSCs. In cases where the limbal niche is damaged, a supportive microenvironment is also needed. Traditional corneal transplantation with penetrating keratoplasty is ineffective (13,23). Without an adequate population of LSCs, corneal transplants cannot re-epithelialize or maintain an intact epithelial layer resulting in rapid opacification or stromal melting of the transplant. The international LSCD Working Group has proposed treatment strategies that depend on the stage of LSCD as outlined in the group’s consensus paper (23). According to the group, for eyes in which vision is significantly compromised and for severe LSCD, surgical treatment that replaces the limbal stem cell population is often necessary to stabilize the ocular surface and improve visual function. These surgeries include conjunctival limbal autograft (CLAU); cultivated limbal epithelial transplantation (CLET); simple limbal epithelial transplantation (SLET); keratolimbal allograft (KLAL); and conjunctival limbal allograft (CLAL) (26).

Transplantation of donor limbal tissue containing donor LSCs using KLAL has been shown to be an effective treatment, as it replenishes LSCs and reestablishes a limbal niche. However, it is a surgically challenging procedure that requires potentially toxic systemic immunosuppression with prednisone, mycophenolate, and tacrolimus to prevent rejection of the highly antigenic limbal grafts. Aggressive blood test monitoring is also required due to the

numerous toxicities associated with the immunosuppressive medications (25,26). Although both SLET and CLET replenish LSCs, they do not reestablish limbal niche, and thus are less effective in patients with extensive damage to the limbus. Because of the complexity of KLAL surgery, only around 100 procedures are performed annually according to the Eye Bank Association of America (EBAA) (27).

Artificial corneas, including the Boston keratoprosthesis (Kpro), have also been used to treat LSCD because they can remain clear in the absence of LSCs and healthy corneal epithelium (28). However, associated complications such as glaucoma, corneal melting, and endophthalmitis have limited the popularity of this procedure (29). In 2022, only 122 KPro procedures were performed in the U.S. based on EBAA reports (27).

BrightMEM Corneal Allograft

Because the limbal niche is critical for corneal epithelial health and healing, any therapy that can regenerate or replace the limbal niche is likely to be helpful in treating LSCD and promoting epithelial regeneration. However, the limbal niche is extremely complex and composed of a unique array of extracellular matrix proteins and supportive cells. Consequently, recreating the entire limbal niche in a diseased eye is nearly impossible without transplanting an entire donor limbus (i.e., KLAL).

As an alternative, treatments that target isolated components of the limbal niche have also been explored for their therapeutic effects. By activating cell signaling pathways normally stimulated by the extracellular matrix and cells of the limbal niche, limbal and epithelial cell proliferation can be stimulated even outside of the native limbus. Several such therapies have already demonstrated some success. Topical application of mesenchymal stromal cells and mesenchymal stromal cell-derived exosomes have been shown to stimulate corneal epithelial regeneration in both LSCD and PECDs (30,31).

The limbal basement membrane is the substrate that supports LSCs and is known to be a critical component of the limbal niche. As part of the extracellular matrix in direct contact with the LSCs, limbal basement membrane provides important cell signaling for LSC survival and proliferation. To date, there has been no available therapeutic replacement for limbal basement membrane. However, recent research has found that DM expresses a number of limbus-specific proteins and is biochemically similar to limbal basement membrane.

Descemet's membrane (DM) is an acellular, naturally occurring basement membrane found on the posterior surface of the cornea. DM is commonly isolated and transplanted intraocularly with donor corneal endothelium for the treatment of corneal endothelial diseases such as Fuchs' dystrophy and bullous keratopathy. Although DM is widely used as a transplant for treatment of endothelial disorders, its application on the ocular surface has not been explored (32).

DM is both optical clear and highly resistant to collagenase digestion, making it attractive as a long-term allograft and substrate for corneal epithelium on the ocular surface. The anterior fetal banded layer of DM shares key compositional similarities with limbal basement membrane, a major component of the limbal niche. These similarities include limbus-specific extracellular matrix proteins such as collagen IV that is restricted to the $\alpha 1$ and $\alpha 2$ subtypes, vitronectin, and BM40/SPARC (33-35). Of these, vitronectin and BM40/SPARC are known to promote proliferation of LSCs and have been shown to induce pluripotent stem cells in culture (34,36).

BrightStar Therapeutics' BrightMEM, an acellular tissue product, is an innovative corneal allograft made from DM. BrightMEM allografts may promote corneal reepithelialization and facilitate corneal epithelial adhesion by providing a favorable and durable type IV collagen basement membrane that can also help protect the underlying stromal tissue. As an acellular, human donor-derived tissue, there is theoretically a minimal risk of rejection. This novel treatment aims to redefine the standard of care for PCEDs and mild to moderate partial LSCD by providing a durable limbal basement membrane-like substrate for promoting LSC and epithelial cell proliferation on the cornea surface. It may also have clinical utility in other moderate to severe ocular surface diseases. The natural collagen structure of BrightMEM is conducive to LSC and epithelial cell survival, growth, and proliferation. It is similar to other therapeutic options such as human amniotic membrane while being optically clear and more durable (32). In vitro preclinical testing data in our labs have shown that, on average, 72% of cells isolated from the limbus of a donor cornea and cultured onto DM maintained their stem cell phenotype, in contrast to about 46% of cells cultured on amniotic membrane. When cultured limbal epithelial cells on DM are induced to stratify and mature into corneal epithelium, cells in the basal layers in contact with DM maintain stem cell-like protein expression, indicating retained proliferative potential. This data suggests that BrightMEM allografts may create an ocular surface environment with improved regenerative reserve, though longer-term studies are needed to confirm this.

BrightMEM allografts are aseptically processed from tissues obtained from donated human corneal tissue according to the FDA's Current Good Tissue Practices regulations. Proprietary techniques are used to remove endothelial cells from the isolated Descemet's membrane without damaging the delicate allografts.

Procedure Overview

The surgery to transplant the BrightMEM allograft is one that will be familiar to surgeons experienced in ocular surface procedures.

- **Prepare the Patient.** Place a speculum in the patient's eye and debride the epithelium or pannus over the cornea out to a diameter at least 0.5 mm wider than the anticipated diameter of the desired allograft. It is important to avoid any overlap of BrightMEM with the peripheral epithelium. Dry the anterior stromal bed thoroughly with a Weck-Cel sponge.

- **Trephine the BrightMEM Allograft.** Trephine the donor corneal button to an appropriate diameter (to a maximum 8.5 mm) to fit within the area of epithelial debridement and then discard the scleral rim.
- **Place the BrightMEM Allograft.** Place the trephined corneal button with the BrightMEM allograft side down onto the cornea surface, staying within the margins of the epithelial debridement. Allow the cornea button to dry in place (approximately 30-60 seconds). Peel the anterior corneal button away, leaving the BrightMEM allograft in place.
- **Smooth Out the BrightMEM Allograft.** The BrightMEM allograft will remain adherent to corneal stroma after the anterior corneal button is removed. If there are wrinkles evident, the surgeon can use a 30-ga cannula to gently sweep over or under the allograft to smooth it out. After the graft is smooth and its orientation is confirmed, wick residual interface fluid out to reestablish good adherence of the allograft.
- **Secure the BrightMEM Allograft.** Place tissue fibrin glue over the graft, taking care to completely cover the edges of the graft. Place a bandage contact lens over the glue and carefully remove the lid speculum without dislodging the contact lens.

Conclusion

Treatment with BrightMEM allografts is a safe surgical procedure that may allow for earlier intervention in patients with epithelial dysfunction to protect against the depletion of LSCs and corneal epithelial cells long term. Other treatments in the toolbox designed to help boost LSC and corneal epithelial cell proliferation such as cenegermin-bkbj (Oxervate; Dompe) and serum tears may be synergistic to BrightMEM allografts. The use of other supportive therapies to maintain the health of the ocular surface (e.g., lubricants, anti-inflammatories) will be needed in concert with BrightMEM.

BrightMEM is not meant for patients who have a complete lack of LSCs. Although unlikely, it is possible for the membrane to dislodge; therefore, the surgical technique requires scraping a wide enough area to ensure the membrane is placed exclusively on the stroma to allow the epithelial layer to grow over it rather than under it. BrightMEM allografts are decellularized, without the endothelium layer, and are derived from older or lower-quality (i.e., inadequate endothelial cell counts) donor corneas that may not be viable for other uses and would otherwise be wasted. This allows for good stewardship of the tissue and fits well with the current infrastructure of eye banking. BrightMEM is also being investigated as a potential treatment for keratoconus and retinal diseases. Future applications may include adding cultured stem cells onto the BrightMEM allograft to treat patients with total LSCD. Future research may extend the use of BrightMEM allografts as a “platform” for other regenerative cell applications in the eye.

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