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Paradigm Shift in Eye Banking: From Tissue Retrieval to Cellular Harvesting and Bioengineering

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Abstract: An integrated cell, tissue, and eye bank is vital to meet the evolving needs of ocular transplant therapies. In addition to traditional corneal transplant tissues, it encompasses processing and delivery of transplant materials for newer treatments like cell-based therapies and gene-modified products, adhering to rigorous standards, optimizing tissue utilization with comprehensive services for surgeons.

Key Words: cornea, cell-based therapies, eye bank, regenerative medicine

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Corneal transplants, although explored for centuries, were first shown to be successful in human eyes by Eduard Konrad Zirm in 1905 when he performed a penetrating keratoplasty in a 45-year-old farmer with bilateral lime burns.[1] The past century has seen rapid advances in the field of eye banking and keratoplasty to improve graft procurement, testing, storage, supply, technique of performing the transplants, and graft survival. However, the availability of donor corneas is currently limited by a global shortage.[2] Efforts are being directed toward maximizing the use of each donor cornea by transplanting individual layers, such as in lamellar surgeries, and further, by transplanting only cells and gene-modifying products.

There have been reports of component corneal surgery being performed using the same donor tissue.[3] Recent years have seen Bowman layer transplants gaining popularity in the management of advanced keratoconus.[4] Similarly, the anterior corneal buttons remaining after Descemet stripping automated endothelial keratoplasty lenticule preparation and lenticules removed in small incision lenticule extraction (SMILE) surgery are being used for various indications such as management of refractive errors (myopia, hyperopia, and presbyopia), tissue augmentation surgeries, and tectonic procedures.[5] Eye banks have now come up with various guidelines to store the extracted lenticules.[6] Cell-based therapies and gene therapies are increasingly gaining momentum and will soon be at the center stage of ocular transplant therapies.[7,8] Cell-based therapies and advanced therapy medicinal products (ATMPs) have made it possible to treat ocular diseases using minimal donor tissue or even cells. These treatment modalities are leading examples of newer advances in targeted therapies for various diseases.

As techniques in corneal transplantation evolve, it is not possible to meet the increasing demands without a parallel evolution in the eye bank structure and practices. The progress in ocular transplant therapies needs a simultaneous progress in the function of eye banks too. Although initially, the eye bank was needed to only preserve the enucleated globe, it now needs to upgrade the structure to meet the current good laboratory practice (GLP) and good manufacturing practice (GMP) standards, for products related to cell-based therapies and ATMPs, which may be derived from extraocular sites.

The functions of an eye bank have thus evolved from being merely a supplier of donor ocular tissue for the surgeons to prepare, to a facility that now prepares, processes, and supplies transplant-ready products not limited to ocular tissues. In this review, we discuss the cell-based products for ocular therapy and the idea of an integrated cell, tissue, and eye bank that is equipped to process all cell-based products and make them available for ophthalmic therapeutic procedures.

CELL-BASED TRANSPLANTS

Epithelial Cells

Cultivated limbal epithelial transplantation (CLET) has been in practice to treat cases of limbal stem cell deficiency.[7]

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A small amount of limbal tissue is obtained from a donor eye and cultured on a scaffold (most commonly either a fibrin gel or an amniotic membrane) to form a sheet of epithelial cells ready to be transplanted. In Asian countries, simple limbal epithelial transplantation (SLET) has gained more popularity considering the economic benefits of the procedure over CLET.[9] In countries like Japan, cultivated oral mucosal epithelial sheet transplantation has been approved for severe ocular surface disorders.[10] Cultivated epithelial cells are a type of ATMP, which are a diverse group of medicinal products used for therapeutic purposes in humans. These consist of somatic cell therapy medicinal products, tissue-engineered products, gene therapy medicinal products (GTMPs), and combined ATMPs (cATMPs), which could be a combination of any of the above-mentioned class of products.[8] The first ATMP to be approved in EU with marketing authorization by the European Medicines Agency (EMA) was the "Holoclar," which is a stem cell–based ATMP, specifically a tissue-engineered product, to treat damaged ocular surface.[11] In Japan, multiple human somatic cell–based products such as "Nepic" have been approved for treatment of limbal stem cell deficiency. The active substance in Nepic is human autologous cornea–derived epithelial cell sheet.[12]

Mesenchymal Stem Cells

Recent studies have explored the role of mesenchymal stem cells (MSCs) in stromal regeneration. Mesenchymal stem cells can differentiate into keratocytes and lay down collagen, affect corneal remodeling, and improve corneal transparency.[13] Mesenchymal stem cells have the potential to promote scarless corneal wound healing and prevent stromal scarring.[14] These MSCs can be sourced from umbilical cord, adipose tissue, bone marrow, dental pulp, and fetal liver.[15] However, extraction of MSCs from these extraocular sites can be cumbersome and tedious. Corneal stroma and the corneoscleral limbus are other important sites from where MSCs can be sourced with relative ease.[14] Recent studies have shown the safety and efficacy of allogenic MSCs in corneal scars and opacities.[16] Clinical trials to assess the effects of MSCs in corneal pathologies are likely to shed more light on the therapeutic effects in vivo and might ascertain the impact on eye bank facilities. Efforts are also being made to expand keratocytes derived from SMILE lenticules and use them as a source of keratocytes.[17]

Endothelial Cells

In addition to epithelial and stromal regeneration therapies, endothelial cell therapies are likely to have the most impact on eye banks owing to the high demand. Endothelial keratoplasties are the most commonly performed lamellar surgeries worldwide.[18] A novel technique to harvest donor endothelial cells and culture them for the purpose of transplant in recipients with endothelial disease has been recently developed. Human cultivated endothelial cells (hCECs) are endothelial cells obtained from a donor cornea and cultivated in vitro. Subsequently, the hCECs are delivered in the form of an intracameral injection and patient is asked to maintain prone position for 2–3 hours to enable the cells to adhere to the posterior surface of the cornea.[19] A clinical trial by Kinoshita et al[20] showed promising results of injecting hCECs with rho-kinase inhibitor as an adjunctive therapy in patients with bullous keratopathy. A major advantage of this approach is that a pool of hCECs can serve multiple patients, easing pressure on the donor endothelial keratoplasty tissue, which is currently used for a single patient in most centers, although 1 donor has reportedly been used for 2 or 4 patients (hemi and quadrant Descemet membrane endothelial keratoplasty). Studies are being conducted to use a tissue-engineered scaffold for the cultivation of these cells and transplant the sheet into the eye after descemetorhexis.[21] Because these are mature differentiated cells, there is still a continued dependance on donor tissue. Preliminary studies have shown induced pluripotent stem cells to have the potential to differentiate into corneal endothelial-like cells when exposed to certain growth factors.[22] Recently, a simple noncultured endothelial cell harvesting technique has been described in a rabbit bullous keratopathy model. This technique harvests functional corneal endothelial cells in a donor cornea with low endothelial cell count, which is otherwise deemed unfit for endothelial transplantation, and these cells are injected into the eye intracamerally.[23] Further clinical trials are needed to assess the efficacy of these therapies and their impact on the need for donor corneas.

ADVANCED THERAPEUTIC MEDICINAL PRODUCTS

The field of ATMPs is currently at the forefront of novel therapeutic approaches for treatment of ocular pathologies that had no prior effective alternatives, such as Stargardt disease, Leber congenital amaurosis, etc.[8] Akin to other medicinal products for therapeutic use, ATMPs must satisfy high standards of methodological and regulatory requirements to be considered safe. Being highly complex in their composition and in the manufacturing processes and authorization, ATMPs pose a challenge to scientists and clinicians alike.[24] The Committee of Advanced Therapies established in 2009 is a multidisciplinary body within the EMA responsible for the advancements in the field, assessment of safety and efficacy, setting standards for quality, and performing evaluation of marketing authorization applications.[25] The classification of ATMPs into various categories as mentioned above is based on the processing needed and the eventual therapeutic effect of the product. The eye is an ideal organ for application of ATMPs for several reasons. It is relatively immunologically privileged and is an organ with relatively small dimensions requiring small amounts of therapeutic products for treatment. Good accessibility to apply treatments effectively and a compartmentalized anatomical structure limiting the effects of the medicinal products to nontarget tissues are additional advantages.[8]

Among the various GTMPs being tested, Vitravene (fomivirsen) was the first GTMP approved by the Food and Drug Administration in 1998, and later by the EMA in 1999.[26] It was an intravitreally administered therapy for

cytomegalovirus retinitis. The second GTMP to receive authorization was Macugen (pegaptanib) for the wet form of age-related macular degeneration. It was approved in 2006 by the Food and Drug Administration and the EMA; however, its use was withdrawn in 2011 for it to be included in the treatment of diabetic macular edema.[8] Luxturna (voretigene neparvovec) is the only commercially authorized GTMP for eye disease. It is indicated in patients with Leber congenital amaurosis and retinitis pigmentosa and is delivered as a subretinal injection.[27] Recently, use of gene therapy has shown potential promise in modifying the expression of mutant genes in Meesman corneal dystrophy, using allele-specific small interfering RNA in human cell lines and intrastromal injection of CRISPR/Cas9 in a mouse model.[28]

Currently, a number of clinical trials are ongoing to assess the efficacy and safety of various ATMPs. In the near future, it is likely that the demand for ATMPs would steadily increase. Apart from ATMPs, significant research is ongoing in the field of retinal transplantation[29] and whole globe transplantation.[30] In such a situation, there is a need for the eye banks to upgrade their facilities to match the standards of methodology and safety necessary for the preservation and distribution of the tissues and organs (Table 1).

EVOLVING EYE BANK STRUCTURE

The eye bank in its most simple and primitive form consisted merely of a room with a refrigerator for storage at 4°C and a thermos flask packed with ice to transport the eyes.[1] McCarey and Kaufman made it possible to prolong the storage time with their corneal preservation medium. Subsequently, development of storage media like K-Sol, Dexsol, and Optisol made it possible to store corneal tissues for 7–10 days.[1] Over the next 50 years, eye banks evolved and had their own equipment such as slit lamp, specular endothelial microscopes adapted to imaging the donor cornea cells, laminar flow hood, preservation media, serology laboratory, and sterilization facilities.[1] The early part of this century witnessed a collaboration between corneal surgeons and eye banks when technicians started getting trained to prepare precut endothelial grafts such as Descemet stripping automated endothelial keratoplasty lenticules and Descemet membrane endothelial keratoplasty scrolls. This meant that the keratoplasty surgery truly started in the eye bank itself and concluded in the operation theatre.

With the recent advances in cell transplants, eye banks dealing with cell-based therapies or ATMPs need to meet the international standards of quality control to ensure safety and efficacy of the final product supplied. The laboratories need to be compliant with the GLP standards and professionals trained in GLP-compliant practices.[31] Similarly, standards of GMP need to be maintained, and the eye banks need to upgrade their infrastructure accordingly.[32]

LOGISTICS AND REGULATIONS

Tissue banking in ophthalmology is unique because other organs in the body (liver, kidney, and heart) are not processed or preserved in a bank before transplantation. Similar to a blood bank, where blood needs to be processed into components and stored for future use, the modern-day eye bank needs to be equipped with facilities to process a single donor corneal tissue into the components needed and maintain the rigorous standards in delivering the transplant tissue. Although conventional eye banks dealt with only tissue harvesting and storage, a modern eye bank dealing with

TABLE 1. Types of Tissues That Can Be Processed, Stored, and Distributed by the Proposed Integrated Cell, Tissue, and Eye Bank

Cells	Tissue	Organ
Limbal stem cells	Ocular tissue	Whole globe
AlloSLET	Corneo-scleral button*	
KLAL*	Cornea	
Cultivated cells	Anterior lamellar cap	
CLET	Bowman layer	
Limbal-mesenchymal stem cells/keratocytes	DSAEK cap	
Human cultivated endothelial cells	Stromal lenticule from refractive lenticule extraction procedures (for correction of myopia, hyperopia, presbyopia, and tissue augmentation in keratoconus)	
	DSAEK lenticule*	
	PDEK scroll	
	DMEK scroll*	
	Sclera	
	Retina	
	Nonocular tissue	
	Amniotic membrane tissue and products	
	Autologous/allogenic serum	
	Umbilical cord serum	

*Tissues that are currently being processed, stored, and distributed by eye banks.

CLET, cultivated limbal epithelial transplantation; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; KLAL, keratolimbal allograft; PDEK, pre-Descemet endothelial keratoplasty; SMILE, small incision lenticule extraction.

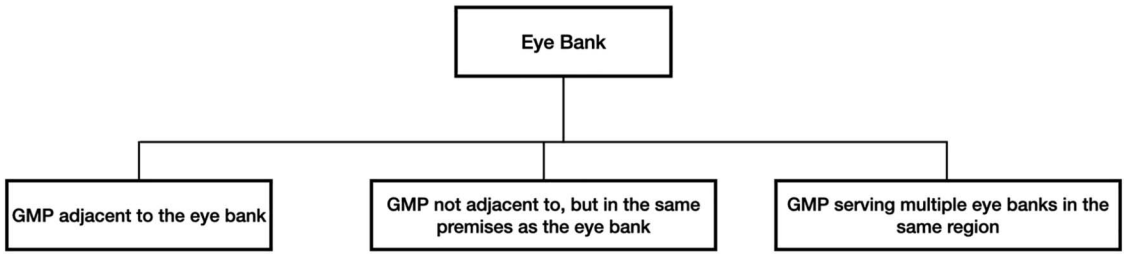

FIGURE 1. An eye bank could have GMP facility adjacent to the eye bank, or in the same premises but not adjacent to the eye bank, or there could be a regional GMP facility for multiple eye banks in a particular region.

cell-based products needs an upgrade to function as a production, storage, and distribution facility of all products derived from the eye and preparing them in a regulated and standardized manner. Most of the products such as limbal MSCs, CLET, and hCECs are exclusive to the eye and are derived from the human tissue itself. It is, therefore, only intuitive to think that an upgrade of an existing eye bank into a GMP or GLP grade facility would make more sense than having conventional eye banks to harvest the eyes, which are the source of the cells, and having a separate cell-based

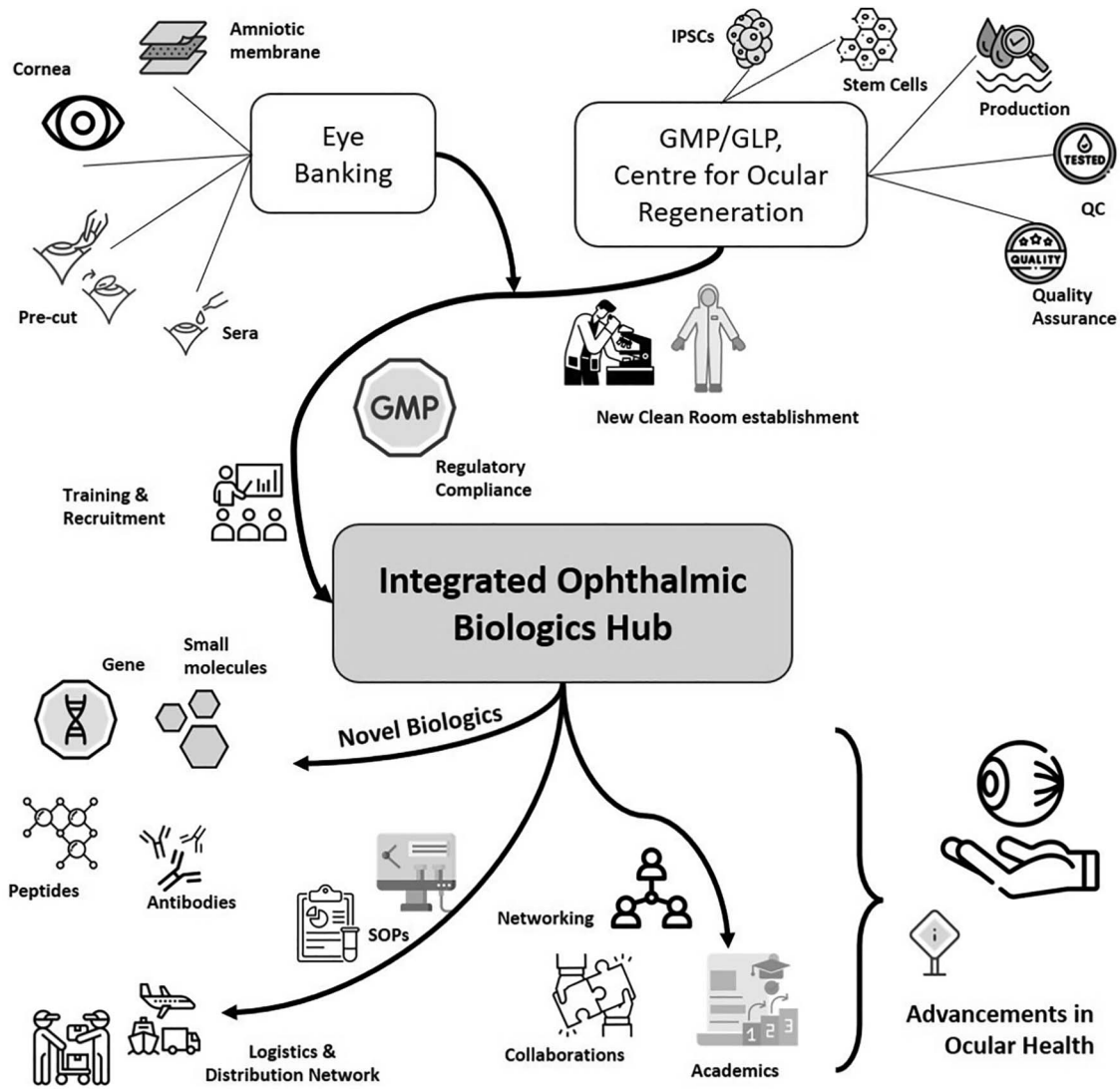

FIGURE 2. Concept of integrated ophthalmic biologics hub taking care of tissue preparation maintaining the good manufacturing practices, training personnel, collaborations, and distribution of tissues ensuring quality control.

products manufacturing unit to process and prepare the cells. Alternatively, eye banks could be associated with a centralized or regional GMP facility that provides for multiple eye banks and for cell therapies in other specialties as a part of its supply network. The idea of a centralized or a regional GMP facility serving multiple eye banks in a particular region would possibly help reduce the cost and administrative manpower needed (Fig. 1). This is a unique opportunity for ophthalmology to improvise on the existing structure of the eye bank and maximize the output. The eye bank today has several elements necessary for manufacturing cell-based products, including, but not limited to, an organizational structure consisting of trained technicians, clean room, quality control teams, and quality assurance teams. In addition, the microbiological and serological testing required before clinical use are needed for both corneal transplants and cell-based treatments as a part of quality control measures. An upgrade of the tissue clean room and a modification of the organogram to meet the GMP and GLP standards are likely to suffice and thus avoid redundancy, considering the similarities in the logistics. The reduced cost of the cell-based product would be an added advantage when the source (corneoscleral rim) and the product (MSCs, CLET, etc) are processed in a single facility (Fig. 2). One major risk, however, that needs to be considered is the possible shutting down of all units at once in the rare event of a contamination.

It is also prudent to consider the regulatory aspects governing transplant of corneas and other ocular tissues. Currently in India, corneal transplants are governed by the Transplantation of Human Organs and Tissues Act (THOTA), 1994.[33] Other tissues prepared and used for ocular treatments such as the human amniotic membrane and the culture media used to store tissues are at present not under any regulatory act in India and perhaps in other developing countries, highlighting the inconsistency and variations that exist in governance regulations globally. Regulations are a means of ensuring standardization and safety of the recipients. However, because the above-mentioned products are unique to ophthalmology, there are no specific regulations in place and these products are currently being prepared and used under the radar of the regulatory agencies. In future, it is likely that as these products are used more often, there might be regulations requiring GMP and GLP compliant facilities to enable standardized preparation. In the absence of an upgraded facility, it is plausible that preparation of these products in the conventional eye banks is brought to a halt. It, therefore, only makes more sense to be prepared for the eventuality when all ocular transplant products are regulated and upgrade the existing eye banks accordingly.

The introduction of ATMPs also introduces the logistical challenge of transport of products under controlled conditions of temperature in a time-sensitive manner and a similar pressure at the receiving center for short-term storage and operating room readiness for application of the product to the patient within the stipulated time. As the cost of production is high, the issue of risks and costs associated with nonusage because of transport, storage, patient, or surgeon factors needs to be addressed. For instance, it is imperative to consider who would assume the financial responsibility in the event of a transportation service failure or if the patient is deemed clinically unsuitable for surgery on the day the product is delivered. The evolution of eye banks to eye laboratories will need to be matched with similar adaptations and developments in logistics, management, and finance.

SUMMARY AND FUTURE DIRECTIONS

We present our vision for the future of eye banking, which must transition from merely supplying corneal and scleral tissues and providing precut and prestripped lamellar grafts, to the procurement and processing of cells, and the production and supply of ATMPs and bioengineered or bioprinted tissues.[34] As the nature of transplanted tissues evolves, there is a concurrent need to upgrade eye bank facilities while maintaining international standards of quality control. The envisioned integrated cell, tissue, and eye bank would encompass all aspects of ocular transplant therapies, catering to the future needs of ocular transplant surgeons, thereby surpassing the current focus on corneal transplant surgeons.

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