Regenerative Engineering and Translational Medicine (2024) 10:172–188
https://doi.org/10.1007/s40883-023-00319-9

REVIEW

Biological Materials Introduced to the Market for Blurred Cornea Regeneration

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Received: 24 April 2023 / Revised: 12 August 2023 / Accepted: 7 September 2023 / Published online: 2 October 2023

Abstract

Purpose Corneal diseases are the fourth reason for blindness around the world which can be treated with corneal transplantation as a gold standard approach. However, alternative strategies get more valuable to peruse due to the challenges of donor shortage and failing the corneal transplantation procedure. This study aims to find the trend of biological products introduced to the market for corneal regeneration.

Methods Biological products introduced by different companies were evaluated in this review. The available and under-evaluation products introduced to market are reported in this review. This search was done by keywords related to corneal/product, corneal/biological scaffold, corneal/biological product, corneal/allograft, corneal/xenograft, eye drops, biological eye drops, and amniotic membrane/cornea.

Results Decellularized products of xenogeneic or allogeneic cornea and amniotic membrane matrixes were mostly employed as corneal scaffold. In addition, biological eye drops, gels, and (platelet-rich plasma) PRP are used in several reports as bioactive ingredients.

Conclusion Herein, the most important issue about biological products that researchers are involved in is preserving the most active ingredients after decellularization or extraction process with minimum modification along with reasonable final cost.

Lay Summary Although at first glance cornea appears as simple avascular collagenous tissue, corneal diseases are the fourth leading cause of blindness according to the WHO reports. Currently, corneal transplantation has been chosen as a gold standard treatment. In recent years, the rising growth of smart biomaterials can be considered as a turning point in modern medicine by using smart scaffolds, a hydrogel with self-healing properties that could be potentially loaded with a drug, autologous cells, or stem cells. Here, we review available and under evaluation products introduced to the market to some extent overcome the cornea transplantation side effects.

Keywords Corneal regeneration · Corneal transplantation · Regenerative medicine · Ocular diseases

Introduction

The transparent and avascular cornea is the anterior segment of the ocular with a thickness of about 575 µm. The cornea is formed in three layers (see Fig. 1); the outer layer is the non-keratinized epithelium that covers the middle layer of stromal connective tissue, and the innermost layer is a cuboidal endothelium. Bowman's layer and Descemet's membrane separate these layers [1, 2]. The epithelium layer of the cornea consists of four to six layers of cells that protect the inner parts of the cornea while being permeable toward oxygen and nutrients to be absorbed into indoor layers [3]. This layer could actively regenerate minor and superficial damages; however, deeper trauma with extension to the

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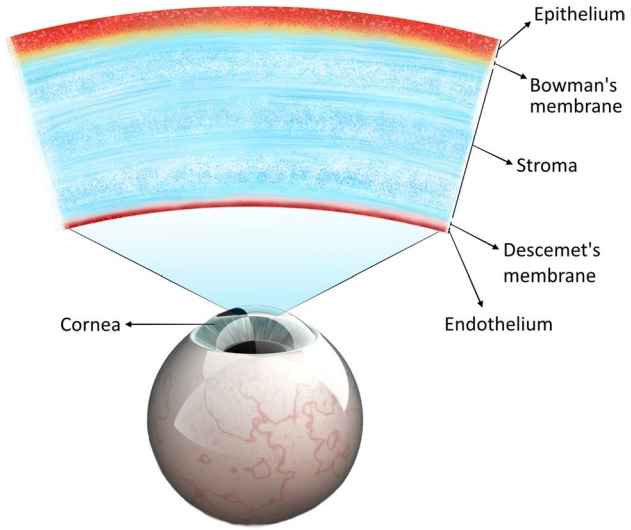

Fig. 1 Corneal structure

stroma leads to permanent opaque scars [4]. About 80–90% of corneal structure belongs to the stromal layer with 500 µm thickness with keratocytes entrapped within aligned collagen fibers [3]. Stromal layers of the cornea disable to regenerate extensive damage into these layers and lead to scar formation which disturbs the hydration of the cornea followed by loss of transparency [3]. One layer of endothelial cells covers the innermost layer of the cornea which pumps out excess fluid diffused by the anterior cornea to avoid the opacity of the cornea; this layer of cornea is unable to repair any damage [3, 4]. The functionality of each layer can be affected by different disorders that are mentioned in Table 1 [1, 5–8].

According to the World Health Organization (WHO), the fourth leading cause of blindness is due to corneal diseases [4, 9]. The most important function of the cornea is due to its radian and perfect transparency for light transmission into the eye which is related to the specific structure of collagenous fibers and the avascular character of the cornea that can be impressed by burn, infection, and trauma [10]. In comparison to other causes of blindness, younger populations are more affected by corneal blindness which is associated with increasing years of disability [11].

Corneal blindness is considered a reversible blindness disease with cornea transplantation [12]. In spite of progress toward corneal transplantation, the rate of undergoing surgery for treatable cases is about one out of seventy people which can be affected by different factors like social, economic, and political factors [11].

The first corneal transplantation was performed by Zirm in 1905 with full-thickness corneal transplantation (penetrating keratoplasty (PK)) which gradually progresses into partial corneal transplantation for selected diseased layers

Table 1 Disorders related to different corneal layers

Diseased layer	Disorders
Corneal epithelial defects	- Limbal stem cell deficiency (LSCD): congenital aplasia of stem cells, Stevens–Johnson syndrome, and ocular cicatricial pemphigoid - Chemical or thermal burn, mechanical trauma, overuse of contact lens, lagophthalmos, foreign body intrusion - Neurotrophic injuries such as severe dry eye, keratitis, nerve damage, diabetes mellitus - Inflammation such as peripheral ulcerative keratitis, autoimmune diseases, infectious keratitis, rheumatoid arthritis, graft-versus-host disease - Systemic or genetic disorders such as dystrophies, Sjögren's syndrome, thyroid eye diseases, and ectodermal dysplasia caused by P63 mutations.
Stromal defects	- Infection - Inflammation - Keratoconus - Neurodegeneration - Neovascularization - Corneal dystrophies
Corneal endothelial defects	- Endothelial dysfunction caused by penetrating or blunt trauma - Corneal decompensation: Fuchs' endothelial corneal dystrophy (FECD), aphakic or pseudophakic bullous keratopathy (ABK/PBK), posterior polymorphous corneal dystrophy (PPCD) - Congenital hereditary endothelial dystrophy (CHED) - Iridocorneal endothelial (ICE) syndrome - Refractory glaucoma - Previous failed corneal grafts - Herpes simplex virus endotheliitis.

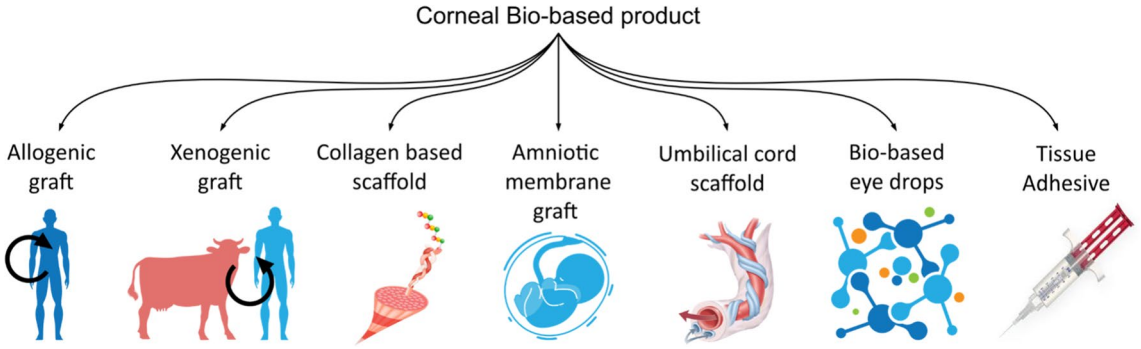

Fig. 2 Biological products in market to regenerate cornea

referred to as partial lamellar corneal surgery [12] which is associated with anterior lamellar keratoplasty (SALK[1], ALTK[2], and DALK[3]) and posterior lamellar keratoplasty (DSAEK[4] and DMEK[5]) [12, 13] with relatively similar outcomes to PK about the complications of pseudophakic bullous keratopathy (PBK), inflammation, and vascularization [13]. In spite of rather satisfying results for these procedures to overcome corneal blindness, there are some noticeable challenges to consider; the shortage of corneas to graft, graft failure, corneal infection, wound dehiscence, and the need for specialized centers to perform this procedure [13–15].

Applying keratoprosthesis is another strategy for corneal diseases that its primary studies began by Doane et al. in 1996 [16]. The artificial cornea was introduced to overcome the shortage of cornea donors and its related complications; however, these constructs are not able to integrate into native tissue and stimulate the biological function of corneal epithelial [2]. In spite of progresses in keratoprosthesis's engineering, a half-life of 3 years was reported for Boston keratoprosthesis [13]; also, complications were reported such as retroprosthetic membrane formation, glaucoma, corneal melting, infectious keratitis, scleritis, suprachoroidal hemorrhages, retinal detachment, endophthalmitis, vitritis, and choroidal effusions and hypotony [17].

Due to the challenges that are ahead for current strategies to restore vision, biological scaffolds have emerged as the decellularized cornea, decellularized amniotic membrane, collagen, umbilical cord, and biological eye drops which are discussed in this review with a glimpse of products.

Materials and Methods

This study provided an overview of the commercially available biological products; however, the cell therapy approaches are excluded from this study as it has been discussed by previous studies [18–20]. This search was done by keywords related to corneal/product, corneal/biological scaffold, corneal/biological product, corneal/allograft, corneal/xenograft, eye drops, biological eye drops, and amniotic membrane/cornea. In this regard, any biological product for cornea which presented as a commercial product is reported in this review. Though, most of the reported products are not FDA-approved and have entered into clinical trials or product markets with desired preclinical results.

Result and Discussion

The quest was performed for commercially available biological products including scaffolds and small molecules for corneal regeneration, except cell-based therapies. Commercially available corneal scaffolds with biological origin are categorized into, allogeneic amniotic membrane, allograft cornea, xenograft cornea, collagen-based matrix, and umbilical cord matrix (Fig. 2) which are discussed in this review (Table 2). In addition, small molecules are presented as biological eye drops and are mostly derived from autologous or allogeneic serum, umbilical cord blood serum, platelet-rich plasma, amniotic extract, amniotic fluid extract, and sodium hyaluronate.

Amniotic Membrane

Reconstructing the ocular surface by human amniotic membrane (HAM) in symblepharon was the first usage of HAM in ophthalmology. Since that, the application of HAM has been increasing for corneal reconstruction in different situations like limbal stem cell deficiency, conjunctival

[1] Superficial anterior lamellar keratoplasty
[2] Automated lamellar therapeutic keratoplasty
[3] Deep anterior lamellar keratoplasty
[4] Descemet's stripping automated endothelial keratoplasty
[5] Descemet's membrane endothelial keratoplasty

Table 2 Biological products for corneal regeneration

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
Amniotic membrane-based products							
AmnioGraft	Cryopreserved HAM	Cryopreservation (Cryo Tek technology) SteriTek® Preservation	- Ocular surface diseases - Ocular transplantation graft	BioTissue/Tissue Tech Inc. (Miami, FL, USA)	NCT02592330	FDA-approved FEI: 3003415347	[34]
PROKERA/ProPro-Kera	Biologic corneal bandage	Cryopreservation (Cryo Tek technology) SteriTek® Preservation	- Keratitis - Recurrent corneal erosions - Filamentary keratitis - Persistent epithelial defects - Neurotrophic corneas	BioTissue/Tissue Tech Inc. (Miami, FL, USA)	NCT00915759/NA NCT05148507/NA NCT04850313/NA NCT00915759/NA NCT02395952/NA NCT02766907/NA	FDA-approved FEI: 3003415347 NIH 510(K): (K032104)	[35, 95]
AmbioDisK	Dehydrated and acellular HAM	PURION Process, Dehydrated	- Non-healing epithelial corneal defects - Corneal erosions - Acute chemical/thermal burns - Eye infections - Dry eyes	IOP Ophthalmics, Inc. (San Ramon, CA)	NCT02395952/NA	FDA-approved HCT/P by US FDA 21 CFR Part 1271	[35, 96]
AmnioTek® AmnioTek®-C AmnioTek™ 2 AmnioTek™-G AmnioTek®-vision	Dehydrated and acellular HAM	Dehydration (DryTek) Decellularization	Corneal surface reconstruction	ISP Surgical CO. LTD. (Bangkok, Thailand)	UMIN000044150/phase IV	ISO 13485 MDR-09052B CTO NO: 100268 CE marked product	[97]
BioDOptix®	Dehydrated and acellular HAM	Dehydration Decellularization	Corneal surface reconstruction	BioDLogics, LLC		HCT/P by US FDA 21 CFR Part 1271	[96, 98]
AmnioClip-plus	Snap freeze fresh HAM	Cryopreservation	- High-risk keratoplasty for limbal stem cell deficiency - Persistent epithelial defects including neurotrophic corneal ulcers (on host cornea/corneal transplants) - …	DGFG	NCT02168790/phase I	PEI.G.11968.01.1. CE approval in Europe	[99, 100]
Omnigen/OmniLenz	Low-temperature vacuum-dehydrated amnion	Tereo® process	Corneal surface bondage	NuVision	NCT04553432/phase IV	NHS OPCS codes of C46.6, C51.5 CE marked product	[38, 101]

Table 2 (continued)

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
Visio-AMTRIX	Dehydrated HAM	Dehydration and devitalization	Corneal surface reconstruction	TBF Genie Tissulaire	NCT05172349/phase II NCT05250583/phase II	ISO 13485 Authorizations ANSM TBF: FR06904T-19-01	[102, 103]
Artacent Ocular	HAM	HAM	- Dry eye syndrome - Filamentary keratitis - Infectious keratitis - Corneal ulcers, ….	Tides Medical®	-	FDA-approved	
Sursight	Dehydrated HAM	Minimally manipulated dehydrated HAM	- Homologous use	SURGENEX®	-	FDA-approved	
Eclipse Tetra slim Tetra thick	Dehydrated HAM	- Air dried - Gamma radiation	Improve surgical outcomes including procedures in Ophthalmology and Optometry	Ophthalogix	-	FDA-approved (HCT/P) (21 CFR Part 1271)	
AmnioMatrix	- Dehydrated AmnioMatrix - Frozen AmnioMatrix	Cryopreservation	- Chemical burns, - Ulcers of the cornea - Conjunctiva - During surgical procedures	Next Biosciences (Johannesburg, South Africa)	-	AABB Accredited ISO 13485	
Aril™	Acellular allograft HAM	Dehydration Decellularization	- Ophthalmology - Orthopedic - Wound covering	SeedBiotech, Inc. (Dallas, USA)	-	FDA-registered by AABB and HCT/P (21 CFR 21 Part 1270 and 1271) ISO11137 ISO10993	
Cell-Amniosin	Freeze fresh cellular HAM	Decellularization Cryopreservation	Cornea surgery	Sinacell Manufacturing Research Company	IRCT20210918052511N1	ISO 13485 GMP IMED 58198445	
Amniosin	Freeze fresh acellular HAM	Decellularization Dehydration	- Bullous keratopathy - Neurotrophic keratopathy - Pterygium repair surgery	Sinacell Manufacturing Research Company	-	ISO 13485 GMP	
Amniodisk	Dehydrated and acellular HAM	Dehydration	- Bullous keratopathy - Neurotrophic keratopathy - Pterygium repair surgery	Sinacell Manufacturing Research Company	-	ISO 13485 IMED 16142643	
Biovance® Biovance®3L Ocular	Decellularized dried HAM	Dehydration Decellularization	Corneal surface reconstruction	Celularity Inc. Verséa Health, Inc.	-	FDA-approved	

Table 2 (continued)

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
Allograft cornea							
OptiGraft	Allogeneic cornea	Gamma irradiated	- Corneal perforation - Corneoscleral laceration repair - Trauma and/or emergency - Boston keratoprosthesis (KPro) - Tectonic anterior lamellar keratoplasty (ALK/DALK)	Lions Eye Institute for Transplant and Research's (LEITR)	-	-	[104]
VisionGraft	- Nano-Thin™ DSEK - Ultra-Thin DSEK (Allogeneic cornea)	- Cryogenically treated - Gamma irradiated	- Corneal melts - Corneal ulcers - Corneal perforations - Tectonic/therapeutic PKP - Anterior lamellar keratoplasty	CorneaGen	NCT04895514/NA	FDA-registered	[50]
Allogeneic corneal graft	Allogeneic cornea		Ocular surface disease and surgeries	Veneto Eye Bank	-		
Xenograft cornea							
ABCcolla Collagen Ophthalmic Matrix (corneal scaffold sheet)	Acellular porcine cornea	ScCO2	Corneal transplantation	ACRO Biomedical Co., Ltd.	NCT04054817/NA	ISO 10993 biocompatibility test (FDA certificate is in the process)	[49]
Decellularized corneal powder (corneal scaffold powder)	Acellular corneal powder	ScCO2	Bioprinting of the 3D cornea	ACRO Biomedical Co., Ltd.	-	ISO 10993 biocompatibility test (FDA certificate is in the process)	
LinkCor	Acellular porcine corneal stromal			LinkoCare Life Sciences AB	NCT04653922/NA	-	[105, 106]
ACORNEA	Acellular porcine corneal stroma		- Corneal ulceration - Replace the impaired tissue of Bowman's membrane	AcuHerb Marketing International Corporation (AMIC)	-	FDA Registration No. MDR-0469	
Xenia corneal implant	Porcine corneal stromal lenticule	Biochemical decellularization process and cross-linking	Keratoconus	Gebauer Medizintechnik GmbH	NCT04741230/NA	-	[85, 107]

Table 2 (continued)

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
Collagen-based products							
FibroGen cornea (FG-5200)	RHC III	HRC III synthesized in yeast and chemically cross-linked	Corneal transplantation	Fibrogen, Inc.	-	-	[52, 53]
Ologen Biocornea	Corneal patch (fish scale derived collagen type I)	Chemical decellularization and decalcification	Patch a perforated, lacerated, or ulcerated cornea for hours up to a few days	Baby Organ Biomedical Corp (BOBC)/ Aeon Astron Europe B.V.	NCT03541551/NA	ISRCTN21989763 EudAMED Number: CIV-15-03-013305	[56, 87]
Ologen Collagen Matrix	Extracellular Matrix (porcine collagen)	Lyophilized and cross-linked type I atelocollagen (≥90%) and glycosaminoglycans (GAG) (≤10%)	Support and modulate corneal repair (wound healing)	Baby Organ Biomedical Corp (BOBC)/ Aeon Astron Europe B.V.	NCT02990143	510(k) Number: K173223 ISO 10993-4,5,6,10,11	[61]
CorVision	Collagen-base bioengineered corneal ilay			LinkoCare Life Sciences AB	NCT04465409/NA	-	
Umbilical cord–based products							
AmnioGuard	Allogeneic umbilical cord graft	Cryopreservation	- Persistent epithelial defects - Corneal surface ulcers - Descemetocele or perforation - Neurotrophic - Bullous keratopathy - Band Keratopathy	BioTissue/Tissue Tech Inc. (Miami, FL, USA)	-	FEI: 3003415347	[66]
Regenesol	AMUC eye gel, drop	Morselized AMUC product in a gel form	Ocular surface diseases: - Dry eye - EPI-off cross-linking - PTK - PRK	BioTissue/Tissue Tech Inc. (Miami, FL, USA)	-	-	[23, 67]
Biological eye drops and gels							
COL - System	Serum, platelet-rich plasma (PRP), and platelet concentrate	Concentrated eye drop		Tissue Bank of France (TBF) Biomed Device s.r.l.	-	-	[108, 109]

Table 2 (continued)

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
OptiSerum	Umbilical cord blood serum eye drop	Centrifugation	- Severe dry eye syndrome with or without primary Sjögren's syndrome - Ocular graft-versus-host disease (GVHD) - Persistent epithelial defects - Chemical burns - Recurrent corneal erosions - Neurotrophic keratitis - Post-LASEK surgery - Post-corneal transplant	Next Biosciences (Johannesburg, South Africa)	NCT04217785/phase I, II NCT01234623 NCT01016158 /NA	-	
COL - System	Serum, platelet-rich plasma (PRP), and platelet concentrate	Concentrated eye drop		Tissue Bank of France (TBF) Biomed Device s.r.l.	-	-	
Genesis Amniotic Cytokine Extract (ACE)™	AME eye drop	Cryopreservation	Ocular surface disease: - Dry eye - Chemical burn - Corneal ulcers - Corneal transplantation treatment - Post-LASEK*	Ocular Science Inc. (Manhattan Beach, CA, USA)	-	-	[23]
Regener-Eyes™	AFE eye drop	d-MAPPS™*	Ocular surface disease	Regenerative processing plant (Palm Beach, FL, USA)	NCT05169931/early phase I	-	[23]
Keera Lyophilized AME	Amnion-derived eye drop	Amnion-derived eye drops; reconstituted with saline	Use in place or following AMT	Veneto Eye Bank (Treviso, Italy)	-	-	[23]
Amnion-derived Cellular Cytokine Solution (ACCS)	Amnion-derived multipotent progenitor cells eye drop	Proteins secreted by amnion-derived multipotent progenitor cells grown to confluency	- Wound healing - Dry eye	Noveome Biotherapeutics (formerly Stemnion), Pittsburgh, PA, USA	-	-	[23]
Vismed	Sodium hyaluronate 0.18%		- Dry eye - Corneal healing	TRB Chemedica (UK) Ltd	-	-	
lagricel® Ofteno	Sodium hyaluronate 0.4%		- Dry eye - Corneal healing	Sophia Laboratories SA De CV	NCT04081610/phase I NCT04704531/phase II NCT04702776/phase IV NCT04704518/phase IV	-	[110]

Table 2 (continued)

Product	Description	Technology	Application	Company	Clinical trial status	Certificate/ISO/trial code	Ref
Hyabak®	Sodium hyaluronate 0.15%		- Dry eye - Corneal healing	Sophia Laboratories SA De CV	NCT04702776/phase IV	-	
Humylub®	Sodium hyaluronate 0.1% chondroitin sulfate 0.18%		- Dry eye - Corneal healing	Sophia Laboratories SA De CV	NCT04702776/phase IV	-	
Thealoz® Duo	Sodium hyaluronate 0.15% Trehalose 3%		- Dry eye - Corneal healing	Sophia Laboratories SA De CV	NCT04704518/phase IV	-	[111]
Tissue adhesive							
Tisseel	Fibrin glue		- Corneal ulcers	Baxter, Vienna, Austria	NCT00155402/phase I	FDA-approved	[112]
Tissucol Duo Quick	Fibrin sealants		- Corneal ulcers	Baxter, Vienna, Austria	NCT02138019/NA	FDA-approved	

ScCO2 supercritical CO2 extraction technology, *PRGF* plasma rich in growth factors, *LASEK* laser epithelial keratomileusis, *d-MAPPS* derived–multiple allogeneic proteins paracrine signaling, *510(k)* US FDA 510(k) premarket notification, *FEI* FDA establishment identification, *HAM* human amniotic membrane, *AMUC* amniotic membrane and umbilical cord, *AME* amniotic membrane extraction, *AFE* amnion fluid extract, *CTO* cells, tissues, and organs, *OPCS* classification of interventions and procedures, *AABB* American Association of Blood Banks, *HCT/P* human cellular and tissue-based products, *PEI* Paul Ehrlich Institute, *DGFG* the German Society for Tissue Transplantation, *Tereo* patented delicate spongy layer removal and evaporation dehydration processes, *TBF* Tissue Bank of France, *ANSM* Agence nationale de sécurité du médicament et des produits de santé, *RHC III* recombinant human collagen type III, *IMED* Iran National Medical Device Directorate

reconstruction, glaucoma surgeries, ex vivo expansion of limbal stem cells, and sclera melt and perforation [21].

The semi-transparent HAM with a thickness of 0.02–0.05 mm is the innermost layer of the placenta which is consisted of three layers; epithelium, basement membrane, and an avascular stroma. The epithelial cells of HAM are responsible for the homeostasis of amniotic fluid along with secretory activity. The permeability of HAM to water and soluble compounds is an important characteristic of this membrane. In addition, secretion of different growth factors, cytokines, and vasoactive peptides (EGF[6], bFGF[7], HGF[8], KGF[9], TGF[10] a, TGF b-1, b-2, and b-3 isoforms, IL-6, IL-8, amniotic IFN-C) makes it an interesting bioactive membrane for its anti-inflammatory, anti-angiogenic, and anti-microbial effects along with promoting epithelialization. Also, HAM is not an immunogenic structure that makes it a proper transparent graft to be transplanted without irritating the immune system to heal corneal wounds while retaining the physiologically moist environment. Following these facts, HAM presented as a suitable substrate for epithelial cells to growth, migration, and adhesion [21–23]. In addition to growth factors and cytokines, other special matrix components in HAM are high molecular weight hyaluronic acid (HA), heavy chain-HA complex, and Pentraxin 3 in a complex (HC-HA/PTX3) that are responsible for the therapeutic effects of HAM. Limbal epithelial stem cells can be expanded ex vivo by maintaining stem cell quiescence in the presence of the complex of HC-HA/PTX3, proving the potential of this complex to reconstruct the limbal stem cell niche [24, 25]. In addition, the anti-inflammatory and anti-scaring properties of HC-HA/PTX3 were proven for ophthalmology applications [26]. Taking the mentioned advantage of HAM, different commercially available HAMs are presented to be used for ocular surface diseases [27–30]. In addition, HAM is introduced as a suitable substrate for in vitro and ex vivo expansion of corneal epithelial cells or a cell vehicle for cultivated limbal stem cells to be transplanted [31–33]. AmnioGraft® is a cryopreserved amniotic membrane presented by BioTissue, Inc. to promote the healing process in corneal ulcers, dry eye, pterygium, chemical burns, excision of tumors, and Stevens–Johnson syndrome [34]. PROKERA® is a biologic cornea bandage that is another cryopreserved product by BioTissue, Inc., based on HAM to reduce inflammation and scar formation during the healing of the damaged cornea [35].

[6] Epithelial growth factor

[7] Basic fibroblast growth factor

[8] Hepatocyte growth factor

[9] Keratinocyte growth factor

[10] Tumor growth factors

BioTissue, Inc. company uses the Cryo Tek technology besides the Steri Tek® preservation technique to bring FDA-approved products of decellularized HAM into the market [36]. However, other processing techniques were introduced by other companies to dehydrate HAM like the PURION Process presented by IOP Ophthalmics, Inc. which prepares the AmbioDisK as a dehydrated and acellular HAM graft [37]. The Tereo® process is another patented process to prepare a dried HAM which is presented by NuVision for products of Omnigen/OmniLenz [38]. Preservation of the biomedical properties of HAM with minimum damage to its structure is the most important issue to consider. It is reported by Cooke et al. [86] that the technology of CRYOTEK® (cryopreservation technology) can preserve the HC-HA/PTX3 as an important biofunctional component that retains the proper functionality of HAM and human umbilical cord (HUC), instead of the dehydration preservation method [34]. However, the dried form of HAM has advantages too; a dried HAM can be stored at room temperature for 2–5 years in free-standing status, but a cryopreserved HAM must be stored at −80°C while attached to a nitrocellulose paper [39]. Though, a recent study by Mao et al. [36] reported the superiority of decellularized dried HAM (Biovance®3L Ocular (Celularity, Florham Park, NJ)) in comparison to dried HAM (AMBIO2® (Katena, Parsippany, NJ)) and cryopreserved HAM (AmnioGraft® (BioTissue, Miami, FL)) in in vitro evaluation for human corneal epithelial cell (HCEC) activity. Different eye banks such as Veneto Eye Bank and Barcelona Tissue Bank provide HAM to graft damaged cornea, however not under a specific trade name.

Allogeneic and Xenogeneic Cornea

Corneal transplantation has been a promising technique for years to restore one's vision, though the risk of failure of transplantation due to immunogenic responses is a concern. In a healthy condition, the risk of immunological rejection for transplanted cornea decreases due to the avascular nature of the cornea and the ocular immune privilege; however, a damaged environment is susceptible to rejecting the transplanted allogeneic cornea due to inflammation and infection [40]. Different decellularization methods have been proposed by various studies to decrease the rejection rate of the transplanted allogeneic or xenogeneic cornea, which is more important in the case of xenogeneic tissues. However, it is important to preserve the native structure and biological factors during any manipulation. Reported strategies for decellularized xenogeneic cornea can be divided into 3 categories: (1) physical methods (high hydrostatic pressure, N2 gas, freeze-thaw, supercritical CO2, electrophoresis), (2) chemical agents (sodium dodecyl sulfate (SDS), Triton X-100, sodium deoxycholate, hypertonic saline, peracetic acid, formic acid, glycerol with chemical cross-linking),

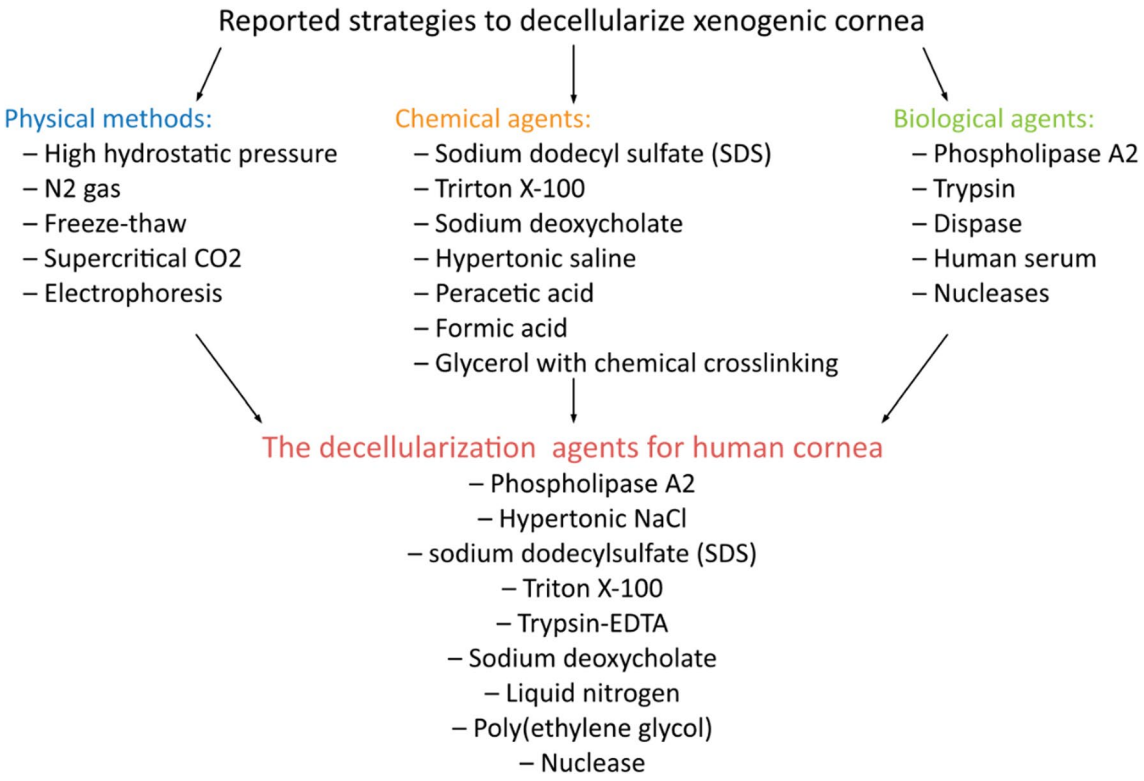

Fig. 3 Different decellularization methods to remove allogeneic or xenogeneic cell components from cornea

(3) biological agents (phospholipase A2, trypsin, dispase, human serum, nucleases) [41, 42]. The decellularization methods for human cornea that were evaluated with different studies are hypertonic NaCl, sodium dodecylsulfate (SDS), Triton X-100 [43–46], trypsin-EDTA [45], sodium deoxycholate [40], liquid nitrogen [43], poly(ethylene glycol) [43], and nuclease [46].

In a comparison study by Huh et al. [45], the superiority of hypotonic trypsin-EDTA to SDS proved for complete decellularization and preserved recellularization of human corneal lenticule. In addition, it is reported by Shafiq et al. [43] that the NaCl decellularized cornea lenticule can support the growth of both epithelial and fibroblast cells, in comparison to SDS-treated cornea that can support the growth of fibroblasts [43, 46]. In a study by Mertsch, sodium deoxycholate monohydrate (NaDC) solution followed by DNase was used for decellularization of the corneal cell sheet derived from human corneal fibroblasts. This decellularized corneal sheet had the property to be implanted into the cornea as a substrate [47].

Different studies compared these methods toward investigation for a proper decellularization method that can conserve transparency and microstructure of decellularized cornea along with the complete removal of cells (Fig. 3). These methods are mostly based on using chemical agents that might damage the extracellular matrix (ECM) and their residuals are toxic. The technology of supercritical carbon dioxide ($scCO_2$) extraction is presented as a great alternative method that can remove cells without toxicity and damage to ECM [48].

Currently, some allogeneic or xenogeneic decellularized corneas are qualified to be commercially available. In ACRO Biomedical Inc., the $scCO_2$ technology is used to decellularize porcine cornea to prepare ABCcolla® collagen ophthalmic matrix. This corneal scaffold is prepared in different thicknesses (20µm, 50µm, 80 µm) to be useable for different corneal transplantation techniques. Also, this company provided decellularized corneal powder for bioprinting applications for 3D structured cornea [49].

ACORNEA® (AcuHerb Marketing International Corporation (AMIC)) is another decellularized porcine cornea that is presented by AMIC ACUHERB Inc.; this product is recommended for cornea ulceration without perforation and replacement of the impaired tissue of Bowman's membrane. Trends toward using allograft cornea instead of xenograft led to the emergence of OptiGraft® cornea by Lions Eye Institute. OptiGraft® (Lions Eye Institute for Transplant and Research's (LEITR)) is a sterile gamma irradiated cornea with a decreased rate of immunological rejection and a long shelf life of up to 2 years. The CorneaGen company introduced another cryogenically treated allogeneic cornea with gamma irradiation sterilization

(VisionGraft) as a substitute for corneal surgery [50]. Mostly, eye banks and institutes introduced acellular allogeneic cornea for corneal transplantation and related surgeries which are not represented as commercially available products.

Collagen

The most abundant structural protein in the cornea is collagen type I; however, other types of collagen are present in fewer amounts. About 70% of the weight in the dry cornea is collagen, because of this fact, collagen is one of the most important choices to be used in corneal tissue engineering. Different studies evaluated different kinds of collagen-based scaffolds. However, there are some challenges ahead for collagenous scaffolds for the cornea as poor mechanical properties and the absence of native fibril structure of corneal stromal, considering the fact that the specific organization of fibrils has a crucial rule in transparency [51].

Previous studies evaluated the efficiency and safety of the human recombinant collagen type III (FibroGen, Inc., San Francisco, USA) for cornea stromal reconstruction [52, 53]. These recombinant collagenous scaffolds are not susceptible to rejection by the immune system and also are safe for disease transmission which is a concern in allografts and xenografts [52, 54, 55]. However, this product is not widely used for cornea stromal reconstruction.

Other sources of collagen which have been used for corneal scaffolds are the porcine cornea and fish scale which have commercially available products. The Ologen® biocornea [56] is a corneal patch based on collagen type I derived from a fish scale that is presented to patch temporarily the perforated cornea for hours to days till a proper donor cornea can be transplanted [57]. Ologen® collagen matrix and implants are derived from the porcine cornea and are presented for different ophthalmic surgeries [58–62]. Xenia® is another collagen-based matrix derived from the porcine cornea that is introduced for keratoconus; this product can be transplanted into the cornea instead of customary cornea transplantation. The Xenia can be prepared for individual patient, as a custom-made device with a rationally simple procedure to implant [63].

Umbilical Cord

The therapeutic effects of human umbilical cord (HUC) blood for cancer and other hematopoietic disorders were proven by different studies and this biologic product is approved by the US Food and Drug Administration (FDA) for lymphomas, leukemia, sickle cell disease, and Wiskott–Aldrich syndrome. However, the biological application of HUC tissue was evaluated later. Similar to HAM, the HUC contains growth factors and cytokines that can promote the proliferation and differentiation of cells along with tissue regeneration and growth [64]. It was the first time in the 1970s that Irving and Herbert used the segments of HUC for skin grafts, science that other studies emerged to introduce other applications of this biocompatible structure for vascular lesion repair, gastroschisis, spina bifida defects, and wound repair [64]. In the case of ophthalmologic surgeries, the efficiency of the HAM-HUC patch was evaluated in reducing the glaucoma shunt tube exposure and showed the properties of low immunogenicity, and high tensile strength with good integration of host-tissue [65].

The AmnioGuard® (BioTissue, Inc.) is an umbilical cord–derived graft that is presented for different ocular surgeries. The high tensile strength and thickness of the AminoGuard® make it easy to handle and suture-able for the reconstruction of the cornea, conjunctiva, socket, sclera, and eyelid [66]. The CRYOTEK® cryopreservation technology is used to prepare the AminoGuard® with preserved properties to reduce inflammation and scar formation along with promoting regenerative healing. Another HUC product is a topical gel, eye drop form of AMUC that is presented by BioTissue/Tissue Tech Inc. with the trade name of Regenesol™, this product should be administrated twice a day for patients with dry eye and after phototherapeutic keratectomy (PTK), EPI-off cross-linking, and photorefractive keratectomy (PRK) [23, 67].

Biological Eye Drops

The crucial rule of growth factors in corneal epithelial regeneration is proven in different studies [68]. Biological eye drops that are rich in growth factors and cytokines from autologous serum [69], allogeneic serum [70], amniotic membrane extract [71], amnion fluid [23], umbilical cord [72], and finger-prick autologous blood [73] can promote corneal regeneration.

The similarity of components in blood serum to natural tears led to the production of serum eye drops for corneal regeneration. The presence of EGF, TGF-β, fibronectin, and vitamin A in serum eye drops promotes corneal regeneration [69]. Rehabilitation of the corneal epithelium occurred via applying the autologous serum eye drop (ASED) to the limbal stem cell deficiency patients [74–76]. In addition to promoting the healing process of corneal epithelial after ocular surgeries [77] and epithelium-off cross-linking [78], the efficiency of ASED is proven with various studies for different ocular surface diseases like graft-versus-host disease (GVHD), dry eye, keratoconjunctivitis, Sjögren's disease [75].

Human platelet derivatives such as platelet-rich plasma (PRP) eye drops, platelet gels, and human platelet lysate are

rich in growth factors (PDGF[11], TGF, EGF, bFGF, IGF-I, HGF, NGF, VEGF[12]) to regenerate the damaged limbal niche [79]. Other bioactive factors for corneal niche reconstruction are based on umbilical cord serum and HAM derivatives. In the case of umbilical cord serum eye drops, substance P, EGF, NGF, and TGF-β are responsible for regenerative effects on the corneal epithelium [72, 80]. Amniotic membrane extracts eye drops are prepared by homogenizing the AM and centrifugation for gathering the supernatant that is full of growth factors [89].

OptiSerum by Next Biosciences is an eye drop derived from umbilical cord blood serum that is rich in growth factors, proteins, and neurotrophic factors to promote corneal healing. The preparation method for OptiSerum is centrifuging the clotted cord blood to separate cellular fractions of serum fraction.

There are different strategies to prepare the HAM eye drops. One of these methods is given step by step as follows: (1) washing the AM (normal saline containing penicillin and streptomycin), (2) using a scalpel blade for chopping into small pieces, (3) submerging in liquid nitrogen, (4) homogenization and centrifugation, (5) collection of the supernatant, (6) centrifugation, (7) sterilizing using a 0.25 mm filter. In other methods, the cryopreserved or dehydrated HAM can be pulverized, micronized, or morselized to prepare the proper HAM extraction as an eye drop. The importance of different processing methods is due to the different amounts of remaining bioactive components in the final products [23]. Another desired biofunction component in eye drops is hyaluronic acid (sodium hyaluronate) which can promote the healing process of corneal wounds by improving cell migration of corneal epithelial cells [81, 82]. Tisseel and Tissucol are two tissue adhesive agents introduced for corneal ulcers to improve healing [83].

Discussion and Conclusion

The scarcity of donor cornea for corneal transplantation as a global issue causes the development of alternative approaches to donor cornea. Regarding the important role of special features in collagen fibers with hexagonal space lattice ultrastructure for presenting the unique optical and mechanical properties of the stromal cornea, most studies rely on allograft or xenograft corneal substitutes. However, these biological scaffolds must be modified toward a proper construct for corneal transplantation to carry the properties of the natural cornea. The main purpose of product processing is to reduce potential risks along with increasing the biofunctionality, biocompatibility, and biomechanical characteristics. Different decellularization methods are applied to the allogeneic cornea to reduce immune rejection, while the proper method must protect the natural ECM components and architecture of the cornea. The importance of decellularization is more concerned in the case of xenogeneic corneal grafts [48, 49, 84]. In addition, cross-linking was introduced to improve the mechanical and functional behavior of a decellularized cornea [85]. In the case of HAM, a proper decellularization method along with a preservation method is crucial to protect the functionality of biofunctional components of HAM [86]. Collagen scaffolds are other introduced alternatives for cornea transplantation. Although fish and porcine collagen are used for commercially available corneal implants, recombinant human collagen can be considered to be a less immunogenic source of biomaterials for corneal implants [52, 53, 56, 61, 87]. Though, the trend of recent preclinical studies can bring insight into the development of natural hydrogels as a corneal substitute, especially hydrogels composed of corneal ECM [88, 89]. Developing bioadhesive hydrogels which can be photo-cross-link to fulfill a defect of cornea is another research near to clinic, known as the sutureless approach, in preclinical research reported as GelCore with satisfying results in rabbit corneal defect [90]. Another promising preclinical study for corneal reconstruction is based on a 3D fiber hydrogel construct. Synthetic polymers of poly (ε-caprolactone)-poly (ethylene glycol) microfibrous are used to mimic the topological structure of the cornea and improve the mechanical properties of gelatin methacrylate (GelMA) hydrogel [91]. Besides a proper scaffold, the rehabilitation of damaged cornea can be achieved via eye drops and gels with regenerative biomolecules. However, most of these products are encountered high production costs and accessibility to good tissue practice (GTP) or good manufacturing practice (GMP) facilities, which are the main limitations of these products; in this regard, a novel intervention by the use of finger-prick autologous blood (FAB) as an accessible alternative for corneal surface diseases is introduced recently [73, 92, 93]. The safety and effectiveness of FAB were proved for severe dry eye disease [73, 92], and the same results were reported by other studies for persistent epithelial defect [93, 94], though, this approach is not categorized as a commercially available product. In spite of introducing several approaches for corneal substitutes, mimicking the specific ultrastructure of corneal stroma or conserving this structure during processing steps is still a crucial concern.

Future Perspective

According to the rising growth of promising results reported in stem cell therapy, smart biomaterials, and artificial intelligence, the integration of these emerging technologies with conventional treatments in corneal disease seems to

[11] Platelet-derived growth factor

[12] Vascular endothelial growth factor

be inevitable. Although at first glance the cornea appears as simple avascular collagenous tissue, the improvement of these limited biomaterials introduced to the market has evoked great expectations due to the lack of long-time functionality or failure transplantation. Stem cell therapies have become a very promising and advanced scientific research topic. A wide variety of possibilities makes this cutting-edge a turning point in modern medicine, such as using smart scaffolds with self-healing properties loaded with autologous cells or stem cells. The role of synthetic biomaterials especially hydrogels with enhanced functional and compatible properties for the improvement of the biological products market also seems to be neglected. Thereupon, a possible snapshot of future commercially available products to overcome the cornea transplantation side effects could be a graft containing a combination of biomimetic synthetic and natural polymers that at least act as transparent mechanical and structural support and cell, drug, and protein carriers.

Funding This study was supported by the Shahid Beheshti University of Medical Sciences (Grant No. 28988).

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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