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Review

Progress in Bioengineering: An Extensive Examination of State-of-the-Art Innovations in the Development of Artificial Corneas

Marco Zeppieri[1,2,*,†], Caterina Gagliano[3,4,†], Fabiana D'Esposito[3,5,6], Mutali Musa[7], Andrea Russo[8], Antonio Longo[8], Rosa Giglio[2], Daniele Tognetto[2], Davide Scollo[9], Federico Visalli[8]

[1]Department of Ophthalmology, University Hospital of Udine, 33100 Udine, Italy
[2]Department of Medicine, Surgery and Health Sciences, University of Trieste, 34127 Trieste, Italy
[3]Department of Medicine and Surgery, University of Enna "Kore", 94100 Enna, Italy
[4]Mediterranean Foundation "G.B. Morgagni", 95125 Catania, Italy
[5]Imperial College Ophthalmic Research Group (ICORG) Unit, Imperial College, NW15QH London, UK
[6]Department of Neurosciences, Reproductive Sciences and Dentistry, University of Naples Federico II, 80131 Napoli, Italy
[7]Department of Optometry, University of Benin, 300238 Benin City, Edo State, Nigeria
[8]Department of Ophthalmology, University of Catania, 95123 Catania, Italy
[9]Eye Clinic Catania University San Marco Hospital, 95121 Catania, Italy
*Correspondence: markzeppieri@hotmail.com (Marco Zeppieri)
[†]These authors contributed equally.

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Abstract

Artificial corneas represent a significant breakthrough in addressing global corneal blindness, impacting millions of individuals worldwide. The scarcity of donor tissue and the complications of immune rejection necessitate the development of synthetic alternatives. This review examines key innovations in biomaterials, scaffold design, and regenerative medicine that have informed the development of artificial corneas. Recent studies have demonstrated that polyethylene glycol (PEG)-based hydrogels exhibit 98% light transmittance and an elastic modulus of 1.5 MPa, whereas collagen scaffolds achieve 85% clinical success with <5% inflammatory response. Graphene oxide-based nanocomposites have increased mechanical strength by 25%. Therefore, by synthesizing clinical and preclinical evidence, this article outlines current achievements and unresolved challenges related to scalability, cost, immune compatibility, and regulatory constraints, providing a roadmap for future translational research in corneal tissue engineering.

Keywords: artificial corneas; bioengineering; tissue engineering; biomaterials; regenerative medicine

1. Introduction

Over the past 20 years, numerous evaluations have examined the progress in artificial corneas, typically focusing on specific components, such as biomaterials, surgical techniques, or preclinical models. Although research has substantially advanced understanding of particular aspects of artificial cornea development, studies have been limited in integrating engineering advances, biological responses, and translational potential. Thus, this review offers a thorough synthesis of materials science, biofabrication technologies, cellular integration, and clinical consequences to address this knowledge gap. Moreover, this study provides a comprehensive overview of the current landscape of artificial cornea research by integrating recent developments, critically assessing the associated significance, and identifying prospective avenues for meaningful advancement.

Corneal blindness is widely recognized as a global health problem, with an estimated 10 million people affected, representing approximately 5% of all blindness worldwide [1]. This burden is particularly pronounced in low- and middle-income countries (LMICs), which face structural challenges in accessing even basic healthcare services and where donor corneas are scarce. Globally, donor corneas are available to fewer than 1 in 70 patients, with sub-Saharan Africa and other regions accounting for <5% of demand [2]. In addition, immune rejection is a major complication of corneal transplantation, affecting about 20% of patients even with advanced immunosuppressive regimens [3]. These limitations highlight the urgent need for new therapeutic strategies that are applicable and accessible worldwide. Recent advances in the treatment of these problems have been driven by discoveries in bioengineering and the development of synthetic corneas.

The pioneering work of Claes H. Dohlman [4], the "grandfather of synthetic corneas", laid the foundation for the field of synthetic corneas. Indeed, this seminal work by Dohlman has subsequently inspired numerous generations of researchers worldwide, even though his methods did not explicitly employ fibroplasia. These efforts have influenced the subsequent development of current bioengineered corneas and have enabled improvements in the de-

sign of synthetic corneas and potential surgical strategies. Subsequent contributions by researchers who have elaborated on the fundamental principles outlined by Dohlman attest to his influence on the field. These contributions include, for example, the hydrogels developed by Chirila in Australia, the biochemical investigations of the *in vivo* responses of prosthetic devices conducted by Trinkaus-Randall, and the advances in collagen tensile strength made by Ruberti and his team at Stanford. Together, these contributions underscore the multidisciplinary and interconnected nature of synthetic cornea development. In particular, substantial progress has been made over the past decade through the development of bioengineered scaffolds that faithfully replicate the structural and functional properties of native corneal tissue. For instance, hydrogels have emerged as highly bioactive materials that are amenable to bioorthogonal chemical modification and have been rapidly and efficiently therapeutically validated in preclinical models [5]. Subsequently, these materials (*e.g.*, polyethylene glycol (PEG)-based hydrogels) exhibit high water content and optical transparency.

Similarly, collagen-based scaffolds, as in the LiQD Cornea project, can replicate the distinct layers of the cornea, thereby conferring the functional characteristics of those layers, adequate mechanical strength, and excellent biocompatibility [6]. Additionally, mixed materials containing nanoscale glass or metallic particles have demonstrated greater strength and resistance to degradation over time, representing a significant advance in durability and longevity. These advancements provide promising therapeutic options for patients in need, particularly in regions with limited donor availability [7]. However, even with these improvements, some issues remain unresolved. In fact, achieving adequate compatibility with the host immune system remains a significant challenge, as even new-generation materials can cause swelling or scarring over time [8]. Another fundamental aspect to be considered and adequately investigated is the long-term stability and optical performance of artificial corneas. In addition, the current scalability and production costs of scaffolds pose significant barriers to the subsequent widespread clinical use of these scaffolds. For example, the production of recombinant collagen scaffolds or nanocomposites entails highly expensive and complex processes, thereby limiting the availability of these scaffolds in resource-constrained settings. Finally, notably, current regulatory frameworks often lag behind rapid technological advances, significantly delaying implementation and clinical use. This review critically examines the current state of artificial cornea development, focusing on three key areas: scaffold design, cell integration, and therapeutic outcomes. In our view, by addressing ongoing challenges and identifying opportunities for innovation, artificial corneas could transform current corneal therapies and expand access to treatment for millions worldwide.

2. Methodology

In drafting this review, we employed a rigorous methodology to identify, select, and critically analyze studies that most significantly contribute to the development of new techniques for the design and use of artificial corneas. Peer-reviewed articles on the development of artificial corneas published between 2002 and 2024 were systematically identified. When deemed necessary for context, foundational studies and recent breakthroughs outside of this spectrum were incorporated. A literature search was conducted in the major academic databases (PubMed, Google Scholar, and Web of Science) using a systematic strategy employing Boolean operators (AND, OR, NOT). For instance, in PubMed, the Boolean combination ('artificial corneas' OR 'bioengineered corneas') AND ('tissue engineering' OR 'biomimetic matrix') was applied to refine the search results. The search strategy included the following key terms: "artificial corneas", "bioengineered corneas", "tissue engineering", "biomimetic matrix", and "corneal regeneration", combined with Boolean operators.

The search was restricted to English-language articles to ensure accessibility and focused on studies with high-quality methodologies and globally relevant findings. Mendeley Reference software was used to manage citations and organize studies systematically. We also sought high transparency and reproducibility in the study selection process.

We included studies that reported significant advances in artificial cornea development, particularly those involving innovative biomaterials, cell integration, and therapeutic outcomes. Specifically, this review covers findings in:

- Materials science: State-of-the-art biomaterials such as hydrogels, collagen-based scaffolds, and nanocomposites with optical transparency, mechanical stability, and biocompatibility [9,10].
- Cellular integration: Papers displaying increased cell binding and growth, plus efficient incorporation of corneal cells into the fabricated constructs.
- Therapeutic outcomes: Studies that evaluated the safety, efficacy, and long-term stability of artificial corneal implants.

Both clinical and preclinical studies were assessed for prospective outcomes. Reviews and meta-analyses were excluded unless they provided novel insights or directly aligned with the objectives of this review. Other studies that focused exclusively on corneal transplants from traditional donors, addressed single biomaterials, or lacked adequate methodological rigor were excluded. A comprehensive search using the criteria described above identified 856 articles in the selected databases. A total of 174 duplicate studies were excluded, and 450 articles were screened based on title and abstract for relevance. Of these, 123 studies were included after a complete-text analysis. Out of 123 included studies, 52 (42%) focused on biomaterial charac-

terization, 47 (38%) were preclinical, and 24 (20%) were clinical trials. To facilitate the analysis of the articles, the studies we selected were classified by methodological approach into the following categories, thereby reflecting the multidisciplinary nature of research on the artificial cornea:

- Experimental studies (42%): These focused on biomaterial characterization and scaffold optimization using advanced techniques such as electron microscopy, atomic force microscopy (AFM), and rheological testing to evaluate mechanical and structural properties.
- Pre-clinical studies (38%): *In vitro* cell culture and animal experiments assessing cellular and tissue ingrowth.
- Clinical trials (20%): Phase 1 studies assessed safety, efficacy, and patient-oriented outcomes, such as the feasibility of collagen-based scaffolds (LiQD Cornea) or PEG-based hydrogels in human subjects.

We conducted a narrative synthesis to identify recurring themes, key innovations, and research gaps, with particular attention to outcomes such as corneal transparency, mechanical strength, immune response, and the ability to restore vision. Table 1 (Ref. [7,11–19]) summarizes key results from selected studies, including the associated objectives, methodologies, primary outcomes, and limitations. These aspects provide a comprehensive understanding of the current state of artificial corneal development and clearly highlight areas requiring further research. Quality assessment was performed to ensure the validity and reliability of the research; we applied standardized quality assessment tools to all included studies, adapting these tools to the specific methodologies employed, including experimental, preclinical, and clinical studies. To ensure methodological rigor and transparency, the included studies were independently assessed by two researchers. Discrepancies in study inclusion were reconciled through consensus.

Specifically, for experimental and preclinical studies, adherence to American Society for Testing and Materials (ASTM) tandards for biomaterials testing was assessed, with specific attention to the reproducibility and robustness of the experimental design [20]. Conversely, clinical trials were evaluated in accordance with the CONSORT guidelines to ensure high methodological rigor, with attention to parameters such as sample size, randomization, blinding, control groups, and duration of follow-up [21]. The risk of bias was mitigated by excluding studies with ambiguous methodology or lacking control groups. Additionally, inter-reviewer concordance was enhanced by an initial calibration step that utilized a subset of randomly chosen papers to standardize rating criteria.

Key assessments included:

- Experimental and preclinical studies: Adherence to standardized protocols (*e.g.*, ASTM standards) and critical evaluation of parameters such as reproducibility and robustness of experimental design.
- Clinical trials: Quality was assessed based on methodological rigor, with randomized controlled trials (RCTs) assigned the highest weight due to the associated robust design.

Through a rigorous, transparent, and reproducible methodology, this review presents a reliable synthesis of current progress in the development of artificial corneas. Furthermore, including studies across different contexts (experimental, preclinical, and clinical) provides a balanced perspective and lays solid foundations for both future research and clinical translation.

3. Material Science

As a fundamental requirement, the design of artificial corneas for human use requires the ability to replicate key characteristics of the human cornea, such as transparency, mechanical strength, and biocompatibility [22]. Recent advancements in stromal tissue engineering have highlighted the potential of innovative techniques to mimic the structure of native corneal tissue. For example, electrospinning enables the production of aligned collagen nanofibers resembling stromal lamellae, thereby improving biomechanical properties while preserving optical transparency [23]. Scaffolds can be classified by material source as natural materials derived from biological sources, synthetic materials designed to possess specific properties, and hybrid materials that combine natural and synthetic components. Recent advances in this area have mainly focused on three key categories of scaffolding materials.

3.1 Scaffolds Derived From Natural Materials

Hydrogels are widely used materials for certain characteristics such as viscoelasticity, optical clarity, and the ability to support cell growth, making hydrogels versatile for corneal scaffolds [24]. Key hydrogel innovations include:

- PEG hydrogels exhibit exceptional transparency (98% light transmission at 550 nm), high mechanical strength (elastic modulus of 1.5 MPa), and high cell viability [13]. Hydrogels can be functionalized with bioactive peptides, thereby improving certain characteristics, such as epithelial cell adhesion and proliferation, by up to 40% relative to scaffolds not functionalized with bioactive materials [14].
- Hyaluronic acid hydrogels are known for their remarkable water retention capacity (approximately 1000% of their dry weight). Meanwhile, hyaluronic acid-based hydrogels can accelerate corneal wound healing in certain preclinical rabbit models, allowing closure of an epithelial defect within 5 days of application [25]. Future studies should focus primarily on the scalability of these hydrogels for human clinical applications.

Table 1. Summary of key findings from selected studies on artificial cornea development.

Study (reference)	Objectives	Methodologies	Primary outcomes	Limitations
Ozcelik *et al*., 2014 [13]	Evaluate PEG-based hydrogels for corneal regeneration	*In vitro* and preclinical assessment of transparency, mechanical properties, and endothelial compatibility	High optical transparency, good biocompatibility, and support for corneal cell survival and regeneration	Swelling behavior and limited long-term mechanical stability
Fernandes-Cunha *et al*., 2020 [11]; Liu *et al*., 2008 [14]	Assess safety and regenerative potential of collagen-based scaffolds	Preclinical and early clinical evaluation of *in situ*–forming or recombinant collagen matrices	Restoration of corneal structure and transparency with low immunogenicity	High production cost and moderate mechanical strength
Chi *et al*., 2023 [19]; Yan *et al*., 2022 [15]	Improve mechanical performance of advanced or hybrid biomaterials	Material characterization and preclinical biological testing	Enhanced mechanical strength with preservation of optical properties and cellular compatibility	Limited long-term *in vivo* validation
Kasravi *et al*., 2023 [7]; Wilson *et al*., 2013 [17]	Evaluate immunogenicity and host integration of decellularized ECM scaffolds	Experimental and preclinical studies of immune response and tissue remodeling	Reduced immunogenicity and improved host cell infiltration compared with cellular matrices	Variability in decellularization quality and scalability challenges
Gupta *et al*., 2019 [18]	Explore gene-editing strategies to reduce transplant immunogenicity	Preclinical studies on CRISPR–Cas9-mediated modification of immunogenic targets (HLA pathways)	Potential reduction of immune recognition and improved graft compatibility	Ethical, regulatory, and safety concerns; early experimental stage
Gómez-Fernández *et al*., 2024 [12]; Xie *et al*., 2024 [16]	Evaluate feasibility and translational potential of 3D bioprinted corneas	Preclinical development and regulatory analysis of bioprinted corneal constructs	High structural fidelity, customizable architecture, and promising optical performance	Limited clinical validation and challenges in large-scale manufacturing

PEG, polyethylene glycol; ECM, extracellular matrix; HLA, Human Leukocyte Antigen.

3.2 Synthetic Material Scaffolds

Collagen is a primary structural protein of the corneal extracellular matrix (ECM) and a fundamental component of scaffolds [26]. Recent advances in collagen-based bioscaffolds include:

- Recombinant human collagen: A multicenter clinical study involving 200 patients reported an approximately 85% success rate in restoring vision over two years, with minimal immunogenic reactions (<5% of patients) [14].
- MicroRNA-loaded collagen films: miR-133b-impregnated collagen films have enabled improved repair and stromal integration of collagen-based bioscaffolds, thereby increasing stromal cell adhesion by 30% relative to conventional collagen scaffolds [12]. However, further confirmation is needed in larger patient cohorts.

3.3 Hybrid Material Scaffolds

Nanotechnology has revolutionized corneal scaffold design by enabling the development of composite materials with superior mechanical and optical properties [27]:

- Graphene oxide scaffolds: In one study, these scaffolds demonstrated good mechanical strength, with approximately 25% increase, and maintained 90% transparency for up to 12 months after implantation in preclinical models [15].
- Silk fibroin nanocomposites: silk fibroin-based scaffolds exhibit high resistance to various biomechanical stresses (up to 1.8 MPa), making these scaffolds ideal candidates for long-term implantation [28]. Further research should focus more on optimizing the biodegradability of these materials.

In conclusion, PEG-based hydrogels are constrained by time-dependent swelling and degradation. Collagen-based scaffolds, especially recombinant variants, are lauded for the associated biocompatibility and reduced immunogenicity, with clinical trials indicating success rates exceeding 85%; nonetheless, the associated low mechanical strength and elevated production costs pose obstacles. Conversely, nanocomposites that include graphene oxide markedly improve durability and structural integrity; however, the associated long-term biocompatibility and potential immune responses remain inadequately investigated.

3.4 Manufacturing Processes

The field of tissue engineering has been revolutionized by three-dimensional (3D) bioprinting, which provides unprecedented precision and scalability for fabricating biomimetic fabrics [29,30]. Moreover, 3D bioprinting enables the fabrication of accurate, functional anatomical structures by combining specific bioinks with high-resolution deposition techniques. Thus, 3D bioprinting is a promising strategy in corneal tissue engineering, as this tool enables the fabrication of scaffolds with a layered architecture that closely mimics the native stratified structure of the human cornea [31]. In addition, another important consideration is the potential for individualized customization of scaffolds.

Notably, 3D bioprinting is based on layer-by-layer deposition of specialized bioinks, thereby enabling the replication of the complex cellular and extracellular composition of the natural cornea [32]. Bioprinting enables high-resolution printing, reaching sub-50 μm, thereby allowing the detailed creation of the different layers of the cornea, including the epithelium, stroma, and endothelium. Furthermore, by being able to use different bioinks such as hydrogels, collagen, and nanocompounds, it is possible to take advantage of the advantages of each compound, such as optical clarity, mechanical strength, and biocompatibility of the native corneal tissue, while limiting the disadvantages of each. Therefore, bioprinting enables the deposition of different materials with distinct properties to create structures with specific functions [16].

Despite the high precision and customizability of 3D bioprinting for scaffold manufacturing, the implementation of this tool in resource-limited settings is hindered by substantial equipment costs, the need for technical expertise, and variability in bioink quality control. These constraints indicate the need for scalable, cost-effective bioprinting technologies tailored to diverse healthcare systems.

3.5 Biological Performance Testing

The promising functional success of artificial corneas depends not only on material properties but also on the associated ability to integrate seamlessly with host tissues and support cellular functions. Recent advances in cell integration include:

- Amphiphilic artificial endothelial layers: Artificial corneas can be coated with bioactive molecules, such as fibronectin; these coatings can improve endothelial cell adhesion by 50% and substantially reduce immune responses in preclinical studies [33]. These coatings can also enhance cell viability and reduce inflammation, making these coatings particularly promising for high-risk patients.
- Bioactive coatings: Heparin-functionalized surfaces can reduce inflammatory markers by up to 30%. In addition, studies in mouse models have shown that surface functionalization with heparin improves stromal cell adhesion [34].
- Dynamic hydrogels: A study conducted *in vitro* on specialized hydrogels that adapt to physiological changes showed a greater capacity to promote stromal cell proliferation by up to 20% than static hydrogels [17].

3.6 Immune Modulation

The long-term success of artificial corneas is highly dependent on immune regulation. Immune-mediated rejection remains a major challenge in the integration and use

of corneal prostheses. Research has shown that proinflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), play a critical role in triggering inflammation that results in immune rejection of corneal implants. These factors promote macrophage activation, T-cell infiltration, and fibrosis. An attempt to mitigate these immune responses employs biomaterial-based immunomodulation strategies. Some experimental models indicate that the superficial functionalization of artificial corneas with heparin or bioactive molecules, such as fibronectin, can significantly reduce inflammation by shifting macrophage polarization toward an anti-inflammatory M2 phenotype. This shift favors a more "immunotolerant" microenvironment. Further support for immune regulation strategies comes from preclinical studies using decellularized ECM scaffolds. These strategies can preserve essential bioactive signals while reducing immunogenic components. In particular, the functionalization of these ECM scaffolds with heparin resulted in a 30% reduction in inflammatory marker expression.

To minimize immune rejection of artificial corneas, innovative strategies have been explored, with promising results. CRISPR–Cas9 gene editing has proven to be a revolutionary tool that enables improvement of transplant compatibility by eliminating the expression of specific HLA (Human Leukocyte Antigen) class I antigens [35]. HLA class I antigens play a critical role in presenting peptides to cytotoxic T lymphocytes, a process central to the immune rejection of transplanted tissues. Therefore, by selectively knocking out the expression of these antigens via CRISPR–Cas9, the tissue becomes 'invisible' to the host immune system, significantly reducing the risk of rejection. Moreover, by selectively modifying the genetic components responsible for tissue immunogenicity, immune rejection rates can be dramatically reduced [35]. Gene-editing approaches based on CRISPR–Cas9 have been proposed to reduce graft immunogenicity by targeting HLA expression, although this strategy remains at an early experimental stage [18]. These results, which are albeit at an early stage, demonstrate the great potential of gene editing to produce immunologically inert artificial corneas, thereby evading host immune detection without the need for systemic immunosuppression. In parallel, decellularized ECM scaffolds have been developed to enhance immune compatibility further, preserving critical bioactive signals required for tissue regeneration and integration [19]. Decellularization techniques enable the removal of immunologically active cellular components while maintaining the structural and biochemical integrity of the matrix, which is essential for corneal regeneration [7].

While CRISPR–Cas9 gene editing provides a highly targeted approach to reducing immunogenicity by modifying the genetic blueprint, decellularized ECM scaffolds offer a non-genetic solution that preserves the native structural and biochemical integrity of the tissue. However, decellularization techniques may still retain residual immunogenic components, necessitating further optimization. Gene editing has shown potential to reduce immunological rejection by modifying HLA expression; however, concerns persist about off-target effects, genomic instability, and the ethical implications of genetic manipulation. Due to the differing regulatory environments across countries, careful advancement, informed by rigorous ethical oversight and extensive safety data, is essential for the responsible clinical use of gene-edited structures.

Both CRISPR–Cas9 gene editing and decellularized ECM scaffolds represent significant advances in the development of the artificial cornea with ideal features for human implantation. In fact, these tools have significant, and perhaps not yet fully understood, potential to overcome the risk of immune rejection and pave the way for safer, more effective, and innovative therapeutic solutions.

4. Discussion

The development of artificial corneas represents a significant advance in addressing corneal pathologies, offering innovative solutions that help meet the ever-increasing demand for tissues. The major technological milestones in synthetic corneal devices over time are summarized in Table 2. Numerous advances in biomimetic scaffold design, cell integration, and the use of innovative materials have laid the foundation for the development of increasingly less invasive therapies [36]. Despite numerous advances, several challenges remain, particularly regarding the production, accessibility, and adoption of these artificial corneas in everyday clinical practice. This review synthesizes recent advances in artificial cornea development, focusing on material integration, regeneration techniques, and translational feasibility. We have sought to identify themes in the literature, including the confluence of biofabrication, smart sensing, and modular design, that inform future developments in the discipline. Technologies such as artificial intelligence (AI)-driven customization and biosensor-integrated implants have shown promise for improved patient-specific outcomes; nevertheless, realistic timelines for their clinical implementation extend until 2030 due to regulatory, infrastructural, and training constraints. Likewise, open-source bioprinting technologies could democratize access; however, these technologies require rigorous validation before widespread implementation. Additionally, these advances should be examined through the lens of translational logistics to improve understanding of the associated potential and constraints.

As noted above, Claes H. Dohlman played a fundamental role in the field of synthetic corneas, and several contributions stem from this pioneering work. In particular, the research by Chirila on hydrogels led to the development of highly bioactive, structurally adaptive materials that enable the design of corneal scaffolds. Meanwhile, in the United States of America (USA), Ruberti and his

Table 2. Key developments in synthetic corneal devices.

Era	Device type/material	Structural advancements	Biological response	Surgical approaches
1960s–1980s	PMMA (polymethylmethacrylate)-based devices.	Basic transparent plastic, limited flexibility.	High rates of rejection due to poor biocompatibility.	Standard open-sky keratoplasty.
1990s	Hydrophilic polymers.	Improved transparency, higher hydration.	Moderate inflammation, occasional fibrosis.	Sutured implants with an improved fit.
2000s	Collagen-based scaffolds.	Layered scaffolds mimicking corneal stromal structure.	Reduced immune rejection, better cell integration.	Suture-free implantation techniques emerge.
2010s	Nanocomposites with metallic or glass fillers.	Enhanced mechanical strength and optical clarity.	Low scarring, improved long-term tissue integration.	Minimally invasive surgical incisions.
2020s	Bioprinted synthetic corneas.	Customizable designs using hydrogels and recombinant collagen.	Minimal inflammation, better epithelialization.	Precision-based laser-assisted surgery.
Future directions	Smart bioengineered corneas with sensors.	Dynamic structures for drug delivery and pressure sensing.	Optimized immune compatibility, real-time monitoring.	Robotic-assisted surgery with real-time imaging.

team at Stanford University provided important characteristics on the tensile strength and biomechanical properties of collagen-based scaffolds [37]. Such research has contributed to the development of synthetic corneal constructs that more closely mimic the mechanical characteristics of native corneal tissue.

Another important contribution comes from Trinkaus-Randall, whose research has been instrumental in understanding biochemical and cellular responses to prosthetic materials [38]. Indeed, this work in particular provided insight into immune modulation and long-term implant integration. This knowledge has significantly improved the biocompatibility of synthetic corneal implants. Other studies conducted in France and Switzerland have carefully examined the integration of scaffolds into the host [39]. Therefore, these studies have enabled improvements in long-term biocompatibility. Of course, no discussion of synthetic corneas would be complete without mentioning the evolution of Boston keratoprosthesis (KPro), originally developed by Dohlman in the 1960s. This device remains among the most widely used corneal prostheses worldwide, with more than 19,000 implants performed to date.

KPro 1 and 2 remain the most widely used synthetic corneal prostheses in the USA. Nonetheless, several promising alternatives are currently under development. Challenges in clinical practice have been underscored by case studies of synthetic corneal use, such as the Boston KPro. For instance, a recent study assessed the results of Boston KPro implantation in 120 patients [40]. The study reported that visual acuity improved in 60% of cases, but a 40% failure rate was attributed to complications. These real-world data provide a foundation for enhancing future designs.

Although Boston KPros have made the treatment of patients with severe corneal disease possible, these devices are associated with long-term challenges. In particular, effects to be considered include the formation of retroprosthetic membranes, stromal thinning, the development of glaucoma, and the risk of rejection due to mechanical and immunological factors. To address these limitations, new-generation synthetic corneas have been designed to improve biocompatibility, optimize host integration, and reduce postoperative complications. These alternatives include AlphaCor™ (Australia) and LucidKPro™ (Canada), which are innovative KPros that have demonstrated strong potential in early clinical trials [41]. AlphaCor™ is a synthetic hydrogel-based keratoprosthesis composed of poly(2-hydroxyethyl methacrylate) (pHEMA), a material capable of guaranteeing high optical transparency. This characteristic allows pHEMA to mimic the physical and refractive properties of native corneal tissue. In addition, unlike polymethyl methacrylate (PMMA)-based rigid KPros, AlphaCor™ promotes integration with the corneal stroma, thereby reducing the risk of extrusion. For instance, researchers at Pohang University have conducted animal studies to demonstrate the high optical acuity and biocompatibility of 3D-bioprinted corneas [42].

Likewise, the AlphaCor™ device has been enrolled in human trials in Australia, with promising results for mechanical stability and transparency [41]. However, some long-term studies have reported a risk of stromal necrosis. Hence, further refinement of material properties and surgical techniques is needed to improve clinical success. LucidKPro™ is a device currently under clinical investigation and represents a new generation of KPro, capable of integrating nano-engineered surface coatings that promote epithelial adhesion, reduce inflammation, and minimize the risk of stromal fusion.

In addition to KPros, it is important to retire the LiQD Cornea project, which represents an innovative biomimetic approach to scaffolding. This project aims to eliminate the need for a rigid KPro through an injectable collagen-

Table 3. Scaffold materials.

Material	Elastic modulus (MPa)	Transparency (%)	Key characteristics
Natural cornea	0.2–1.5	98	High flexibility, native biomechanical structure.
PEG-based hydrogels	1.0–1.5	95–98	High water retention, optical clarity.
Collagen scaffolds	0.5–1.2	90–95	Biocompatible, mimics stromal structure.
Nanocomposite scaffolds	1.2–2.0	90	Enhanced mechanical strength and durability.

based hydrogel for stromal regeneration. This system comprises liquid collagen hydrogel formulations that self-cure *in situ*, thereby enabling the creation of a structurally stable scaffold that integrates with the corneal stroma. Preclinical studies have demonstrated the ability to restore corneal transparency and excellent biomechanical properties, making it a promising alternative for treating certain corneal disorders, such as moderate-to-severe corneal thinning, without requiring a full-thickness transplant [39].

The safety and efficacy of artificial corneas have been evaluated through clinical trials. For example, phase I/II trials of corneal LiQD have reported an 85% success rate in restoring corneal clarity over two years, with less than 5% of patients experiencing deleterious immune responses [43]. Similarly, a phase III trial of the Boston KPro 1 showed that 60% of patients experienced an increase in visual acuity. However, retroprosthetic membrane formation remains one of the most common complications after Boston keratoprosthesis implantation, with reported incidence rates ranging from approximately 30% to 50% in large clinical series [40].

The future integration of bioprinting technologies and advanced materials is anticipated to facilitate the production of synthetic corneas that are more cost-effective and reliable. We expect that by 2030, devices such as the LiQD Cornea and LucidKPro™ will become viable alternatives to the Boston KPro, providing superior results and addressing current market gaps.

A comparative analysis of prominent artificial cornea designs highlights the individual benefits and drawbacks of each design. The Boston KPro, while widely used and clinically validated, is associated with long-term complications, including the development of a retroprosthetic membrane and glaucoma. Conversely, AlphaCor, a hydrogel implant, enhances integration with host tissue but poses a danger of stromal necrosis. Recently, LucidKPro has demonstrated encouraging preliminary outcomes through nano-engineered surfaces that reduce inflammation and improve epithelial adhesion, although long-term clinical data remain scarce. These comparisons highlight the need for advanced designs that integrate mechanical durability, biocompatibility, and long-term stability while mitigating associated challenges.

In the design of artificial corneas, several components such as hydrogels, collagen-based structures, and nanocompounds have emerged as fundamental scaffolding materials. The key mechanical and optical properties of the main scaffold materials compared with native cornea are summarized in Table 3. Each of these components has advantages and limitations. Hydrogels, especially those based on PEG, are characterized in particular by high long-lasting transparency (98% light transmission at 550 nm) and mechanical properties that are very similar to native corneal tissue (elastic modulus of 1.5 MPa) [19]. Furthermore, functionalizing these hydrogels with bioactive peptides can improve the subsequent adhesion and proliferation characteristics by up to 40% [44]. However, a significant limitation of hydrogels is the associated tendency to swell and degrade under certain environmental conditions, which poses a challenge that should be addressed, particularly for long-term use. Similarly, recombinant collagen scaffolds have excellent biocompatibility and efficacy in use. The success rate of restoring good vision within two years can be as high as 85% [45].

In addition, recombinant collagen scaffolds exhibit lower immunogenicity than human donor-derived corneas, thereby reducing the risk of rejection after transplantation. Despite these promising results, the current potential use is substantially constrained by the high production costs of recombinant collagen, particularly in settings with limited economic resources or, in any case, for large-scale applications. Within the large category of collagen-based scaffolds, collagen vitrigel membranes (CVMs) faithfully replicate the optical and mechanical properties of the cornea. Compared with traditional collagen scaffolds, such as recombinant collagen or microRNA-impregnated collagen films, CVMs offer a unique combination of high transparency, ease of surgical handling, and biocompatibility. For instance, the transparency of CVMs (up to 94%) exceeds that of currently used membranes, and their tunable thickness enables seamless integration with host tissue. Furthermore, preclinical studies have demonstrated that CVMs can promote corneal endothelial cell proliferation and partially restore corneal transparency in animal models [8]. Despite these advantages, CVMs have limitations.

One of the main limitations is the need to standardize production protocols to ensure the reproducibility of desired characteristics. In addition, further studies are needed to adequately assess the long-term durability of CVMs and their capacity to prevent complications, such as immune rejection and fibrosis. Currently, CVMs represent a po-

tential bridge to more advanced solutions; however, the adoption of these membranes in clinical practice will depend primarily on future research that addresses these challenges. Several preclinical studies have validated the potential use of engineered scaffolds for corneal stromal regeneration. Electrospun scaffolds have been shown to ensure optimal cell proliferation and stromal integration. In addition, chemically modified hydrogels were tested *ex vivo* to enhance nutrient diffusion and cellular interactions, thereby providing a robust platform for corneal tissue engineering [46].

Nanocomposites, such as graphene oxide-integrated structures, are characterized by excellent mechanical strength and have shown improvements of about 25% in the strength of the nanocomposites compared to scaffolds composed of collagen [47]. However, the potential immune responses that may determine the nanoparticles used have yet to be investigated at the molecular level. The individual limitations of each material can be overcome by designing hybrid scaffolds that combine the advantages of these materials, such as the transparency of hydrogels, the biocompatibility of collagen, and the mechanical robustness of nanocomposites.

These multifunctional scaffolds would help fill existing gaps, but large-scale production would need to be optimized to improve cost-effectiveness and scalability. Finally, a critical development linking structural and therapeutic applications is the integration of engineered scaffolds with drugs to enable localized and sustained release. The integration of drug-delivery systems into bioengineered corneal scaffolds is an emerging approach that provides dual therapeutic and regenerative functions, addressing long-standing limitations in traditional corneal treatments. In particular, hydrogel-based compounds and nanocomposites have proven effective for delivering therapeutic agents to corneal defects. In preclinical models, hydrogels laden with anti-inflammatory agents substantially reduced postoperative inflammation and accelerated epithelial healing [19]. These results emphasize the therapeutic potential of integrating regenerative scaffolds with drug delivery. For example, studies of hydrogel-based compounds enriched with platelet-rich plasma (PRP) reported faster closure of epithelial lesions in rabbit models than in untreated controls [48].

These tests suggest an important potential for accelerating corneal wound healing. Conversely, the incorporation of drugs or growth factors allows all subsequent actions to be conducted selectively. In particular, the sustained release of growth factors, such as fibroblast growth factor (FGF) or vascular endothelial growth factor (VEGF), is secondary to the gradual degradation of the scaffold matrix, which, in turn, is driven by the enzymatic activity present in the corneal microenvironment. The use of this re-release system guarantees a localized therapeutic effect that allows for minimizing systemic exposure to these drugs [49].

One of the most important advantages of these systems is their ability to maintain desired concentrations for extended periods. For example, *in vitro* PEG-based hydrogels have been designed to release anti-inflammatory agents, such as dexamethasone, for up to 72 hours, thereby reducing the need for frequent applications [50]. However, applying these promising approaches *in vivo* in clinical practice, achieving programmed, highly controlled release kinetics, remains particularly difficult due to variations in enzyme activity and local environmental factors that significantly alter the rate of scaffold degradation. In addition, compatibility between the scaffold material and the drug is critical; certain therapeutic agents may lose stability upon incorporation into specific polymer matrices, thereby reducing efficacy [51].

From a clinical perspective, drug-scaffold systems could be transformative for the treatment of many chronic corneal diseases, such as keratitis, in which prolonged therapy is often necessary to prevent recurrences or fibrosis [52]. Similarly, incorporating antibiotics into scaffolds could provide a therapeutic strategy to combat various corneal infections and promote corneal regeneration. Some preclinical studies have yielded promising data [53]. Meanwhile, it has been noted that silk fibroin scaffolds loaded with antibiotics inhibit bacterial growth for up to seven days and support the proliferation and alignment of stromal cells, thereby promoting optimal repair [54]. However, obstacles remain in the scalability and reproducibility of these systems.

Despite unresolved challenges, the prospect of integrating active drugs into scaffolds represents an important step forward in individualized medicine. This type of approach would, on the one hand, enable localized therapy and, on the other, improve compliance and outcomes.

4.1 Future Directions

The development of hybrid scaffolds that integrate the complementary properties of different biomaterials remains a promising direction. Functionalized nanocomposites and bioactive coatings have the potential to further improve cell integration, mechanical strength, and optical transparency, thereby addressing some of the limitations of current approaches [55]. Innovations and the use of 3D bioprinting and automated synthesis techniques would significantly reduce the cost of producing artificial corneas and improve scalability [16]. In addition, open-source bioprinting platforms have demonstrated the ability to produce customized implants while reducing costs relative to conventional methods [56].

Another tool that could be used in the future is the development of AI-based algorithms trained on specific corneal image datasets. These tools would enable the design of customizable bioscaffolds alongside the potential to build scaffolds that adapt to the corneal anatomy of each individual, thereby enabling tailored solutions for the pa-

tient. Moreover, the use of AI-based imaging technologies during surgery could help improve the surgical accuracy of their placement by providing real-time integration analysis.

4.2 Ethical Considerations

The ethical implementation of artificial corneal technologies necessitates adherence to the principles of autonomy, beneficence, non-maleficence, and justice. Patient autonomy must be maintained through transparent, informed, and culturally attuned consent procedures, especially in clinical trials involving genetically engineered entities or innovative implants [57]. The notion of fairness underscores the necessity of rectifying inequalities in access to advanced technological solutions between affluent and resource-constrained regions. Moreover, responsible innovation necessitates open regulatory discussions that consider global viewpoints, particularly those of marginalized groups. These ethical frameworks are crucial for ensuring equitable and safe clinical translation of next-generation corneal replacements [58].

5. Conclusions

This study offers a thorough synthesis of current progress in artificial cornea production, using concepts from biomaterials science, regenerative medicine, immunological engineering, and translational strategies. While prior work has examined individual elements, our approach integrates multiple developments to provide a comprehensive view of current capabilities and future challenges. By recognizing constraints in scalability, immunological responses, ethical implications, and regulatory preparedness, this review offers a framework for the responsible advancement of the field. Despite their promising regenerative potential, numerous innovations remain in the early stages of validation, and realistic forecasts must account for both scientific promise and systemic obstacles to implementation. Ongoing interdisciplinary collaboration and ethical oversight will be essential to realizing the full potential of artificial corneal implants.

The field of artificial cornea development has made remarkable progress, ushering in a transformative era in the treatment of corneal pathologies. This review highlights several current fundamental innovations, including PEG-based hydrogels with good optical clarity, recombinant collagen scaffolds that have been shown to restore vision, and nanocomposites with high mechanical strength and biodegradation resistance. Unlike previous reviews, this work summarizes key advances in artificial cornea development and proposes strategies to address current limitations. Challenges such as immune compatibility, high production costs, and scalability remain critical barriers to the widespread adoption of artificial corneas, necessitating targeted strategies to overcome them. Some emerging technologies, such as 3D bioprinting and smart biosensor-enabled implants, offer promising avenues to overcome many of the limitations of current production methods. For example, the use of bioprinted corneas would reduce production costs by up to 40% while maintaining 95% optical clarity.

Nevertheless, significant challenges remain. To prevent these innovations from being stifled, robust guidelines for the production of artificial corneas and strict regulatory frameworks are needed to support the development of numerous, ever-increasing innovations. Even ethical considerations, and in particular those concerning CRISPR–Cas9 and nanocomposites, require transparent and globally shareable decision-making processes. Future artificial corneas are poised to redefine the treatment of corneal pathologies by the end of the next decade. Indeed, by 2030, 3D bioprinting will have the potential to enable on-demand fabrication of corneas tailored to the pathology of the individual patient, thereby drastically reducing the current dependence on donor tissue. Meanwhile, by 2035, biosensor-enabled implants could become a clinical reality, enabling numerous real-time measurements, such as intraocular pressure and immune responses, to help minimize postoperative complications. Owing to ongoing innovation and global collaboration, artificial corneas have the potential to revolutionize ophthalmology in the near future.

Author Contributions

Conceptualization, MZ, CG, FD, DT, and FV; methodology, MZ, CG, FD, MM, AR, RG, AL, DS, DT, and FV; investigation, MZ, CG, FD, MM, and FV; resources, MZ, CG, DS, DT; data curation MZ, CG, FD, MM, AR, AL, DS, DT, and FV; writing—original draft preparation MZ, CG, FD, MM, and FV; writing—review and editing, MZ, CG, FD, MM, AR, AL, DS, DT, and FV; visualization, MZ, CG, FD, MM, AR, RG, AL, DS, DT, and FV; supervision, MZ, CG, DS, DT; project administration, MZ, CG, DS, DT. All authors have read and agreed to the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Caterina Gagliano is an affiliate of the Mediterranean Foundation "G.B. Morgagni"; the judgments in data interpretation and writing were not influenced by this relationship.

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