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Commentary
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Precision Anti-VEGF–Releasing Endothelialized Amniotic Membrane Patches for Corneal Neovascularization

Abaidullah Shaukat[1,2], Abeeha Munir[1], Zainab Riasat[1], Momina Niazi[3]

[1]Quaid-e-Azam Medical College, Bahawalpur, Pakistan

[3]Services Institute of Medical Sciences, Lahore, Pakistan

[2]Corresponding Author Email: abaidullahshaukat@gmail.com

ABSTRACT

Corneal neovascularization (CNV) is a vision-threatening complication of inflammatory, infectious, ischemic, and traumatic corneal disease. Vascular endothelial growth factor (VEGF) plays a central role in both hemangiogenesis and lymphangiogenesis in the cornea, and anti-VEGF agents have demonstrated efficacy in reducing pathological vessel growth. However, current delivery strategies are limited by rapid clearance, poor tissue retention, and the need for repeated administration. Amniotic membrane (AM) transplantation, widely used in ocular surface reconstruction, possesses intrinsic anti-inflammatory and anti-angiogenic properties but provides only transient suppression of neovascularization. This Perspective presents a conceptual, non-experimental design framework for next-generation biofunctionalized, anti-VEGF–eluting AM patches to achieve sustained, localized angiogenic inhibition while preserving optical clarity and ocular surface compatibility. We critically position this approach relative to existing AM-based and non-AM delivery platforms, outline key engineering and biological design considerations, and discuss translational, regulatory, and feasibility challenges. While experimental validation is required, this framework integrates advances in biomaterials engineering and ocular pharmacology to inform future development of precision CNV therapies.

Keywords: *corneal neovascularization; amniotic membrane; anti-VEGF; bevacizumab; ranibizumab; aflibercept; drug-eluting patch; ocular tissue engineering; lymphangiogenesis*

1. Clinical need and translational opportunity

Corneal neovascularization represents a pathological breach of corneal immune privilege and avascularity, leading to stromal scarring, lipid deposition, reduced visual acuity, and increased risk of graft rejection following keratoplasty. Common etiologies include infectious keratitis, chronic inflammation, limbal stem cell deficiency, chemical injury, and hypoxia related to contact lens wear. Current management strategies, including topical corticosteroids, laser photocoagulation, and anti-VEGF therapy, are often limited by incomplete efficacy, adverse effects, or the need for repeated interventions (1,2).

Anti-VEGF agents such as bevacizumab and ranibizumab reduce corneal vessel density when administered topically or subconjunctivally, yet their clinical utility is constrained by short ocular surface residence times and variable penetration into stromal tissue (1,3). In parallel, AM transplantation has become a mainstay of ocular surface reconstruction due to its anti-inflammatory, anti-fibrotic, and epithelial-supportive properties (4). These observations create a translational opportunity to

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integrate sustained anti-VEGF delivery within an AM-based scaffold, addressing both the molecular drivers of angiogenesis and the structural requirements of ocular surface healing.

2. Angiogenic and Lymphangiogenic Biology in CNV:

VEGF-A is a major mediator of hemangiogenesis in CNV, promoting endothelial proliferation, migration, and increased vascular permeability. However, lymphangiogenesis, largely driven by VEGF-C and VEGF-D signaling through VEGFR-3, also plays a critical role in immune cell trafficking and graft rejection following corneal transplantation (5). Selective VEGF-A blockade may therefore incompletely suppress the full neovascular response.

Clinical and experimental studies demonstrate that anti-VEGF agents reduce corneal vessel length and density, but adverse effects, including delayed epithelial healing, corneal thinning, and epithelial toxicity, have been reported, particularly with repeated topical administration (2,3). These limitations highlight the need for localized, sustained, and lower-dose delivery strategies that minimize off-target exposure while maintaining therapeutic efficacy.

3. Amniotic Membrane as a Bioactive Scaffold:

Human AM consists of a basement membrane and an avascular stromal matrix rich in collagen, laminin, fibronectin, and growth factor–modulating proteins. In addition to pigment epithelium-derived factor (PEDF), AM contains thrombospondin-1 (TSP-1) and tissue inhibitors of metalloproteinases (TIMPs), which collectively suppress angiogenesis, inflammation, and extracellular matrix degradation (4,6).

Clinically, AM transplantation reduces CNV via a combination of mechanical coverage and the release of bioactive factors. However, its anti-angiogenic effects are transient and highly dependent on processing, preservation, and degradation kinetics. Engineering AM as a controlled drug-delivery scaffold represents an opportunity to extend and potentiate its therapeutic effects.

4. Design Framework for a Biofunctionalized Anti-VEGF–Eluting AM Patch:

This Perspective proposes a design framework rather than a fixed construct, emphasizing tunable parameters that can be adapted to different clinical scenarios.

4.1 Sustained Local Anti-VEGF Delivery:

Prior in vitro studies have shown that AM can adsorb and retain biologically active bevacizumab, with VEGF-blocking activity preserved for days to weeks (7). Based on reported adsorption capacities, clinically relevant loading on the order of 10–50 μg/cm² is theoretically achievable without compromising membrane integrity. Release kinetics may be modulated through crosslinking density, membrane thickness, and incubation concentration. Sustained surface delivery may partially overcome tear film turnover, which removes approximately 16% of surface drug per minute, by maintaining a local drug reservoir at the corneal interface.

4.2 Surface Biofunctionalization and Biocompatibility:

The term *endothelialization* has been inconsistently applied in ocular biomaterials literature and is avoided here. Instead, surface biofunctionalization refers to cell-free or non-angiogenic modifications designed to enhance epithelial compatibility, reduce fibrosis, and minimize inflammatory responses. Importantly, vascular endothelial cell seeding is explicitly excluded, as it would be biologically counterproductive in an anti-angiogenic application. Biofunctionalization strategies may include decellularization, extracellular matrix stabilization, or incorporation of anti-inflammatory and anti-fibrotic cues while preserving optical transparency.

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4.3 Degradation, Adhesion, and Optical Constraints:

Controlled degradation is essential to balance therapeutic residence time with the avoidance of long-term persistence of foreign material. Crosslinking and preservation methods can extend residence from days to several weeks. Patch adhesion may be achieved using fibrin glue or inherent AM adhesiveness, minimizing suture-related inflammation. Any modification must preserve corneal transparency, which remains a non-negotiable requirement for clinical translation.

5. Comparison With Existing and Emerging CNV Therapies:

Compared with topical drops and subconjunctival injections, AM-based drug-eluting patches offer prolonged local exposure with reduced dosing frequency. Drug-eluting contact lenses and hydrogel corneal patches provide similar sustained delivery but lack the intrinsic bioactivity of AM (8). Nanoparticle formulations and microneedle approaches improve penetration but raise concerns regarding toxicity and manufacturing complexity. Gene therapy offers long-term suppression but faces substantial regulatory and safety barriers. A biofunctionalized AM patch occupies a middle ground in translational research, combining established surgical familiarity with advanced drug-delivery engineering.

6. Preclinical Evaluation Roadmap:

- In vitro studies should quantify drug loading (μg/cm²), release kinetics, and functional VEGF inhibition using endothelial proliferation and migration assays.
- Small animal models, such as rabbit alkali burn or suture-induced CNV, are appropriate for assessing vessel density, lymphangiogenesis, epithelial healing, and optical clarity over 2–6 weeks.
- Large animal studies may validate scale-up, surgical handling, and visual outcomes in anatomically relevant models prior to clinical translation.

7. Clinical and Regulatory Considerations:

This technology would likely be regulated as a combination product under 21 CFR Part 3, with classification determined by its primary mode of action. Manufacturing considerations include sterility, storage stability, and batch-to-batch reproducibility. Early-phase clinical trials should prioritize safety, corneal clarity, and pharmacodynamic endpoints, with CNV area reduction and visual acuity as secondary outcomes.

8. Challenges and Future Directions:

Key challenges include optimizing drug loading without compromising transparency, predicting release behavior under dynamic tear conditions, and addressing lymphangiogenic pathways beyond VEGF-A alone. Future iterations may explore combination strategies targeting VEGF-C/D or the integration of anti-fibrotic agents. More speculative concepts, such as VEGF-responsive release systems, should be considered exploratory and require substantial validation.

9. CONCLUSION:

Biofunctionalized, anti-VEGF–eluting amniotic membrane patches constitute a rational, clinically grounded approach to addressing the limitations of current CNV therapies. By integrating sustained molecular inhibition with a biologically active scaffold, this approach may reduce treatment burden and improve long-term outcomes. Experimental validation is required, but the framework outlined here provides a structured roadmap for future development in ocular tissue engineering.

AI Use Statement

Artificial intelligence tools were used for language refinement and structural editing. No AI tools were used for data generation, analysis, or interpretation.

Conflict of Interest

None declared.

Ethical Statement

Not applicable.

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