

Regenerative Biomedicine

Production and Hosting: Shahid Sadoughi University of Medical Sciences

Journal homepage: jrb.ssu.ac.ir

Review Article

3D Printed InVitro Models of the Blood-retinal Barrier to Study AMD Mechanisms

Ali Reza Mofakhami Pourmehrabadi [1], Mohamad Negahi [1], Bibi Fatemeh Haghiralsadat [2], Fatemeh Kuchakzade [3,4*]

1- NanoBiotechnologists Fardanegar Co., Yazd Science and Technology Park, Yazd, Iran.

2- Stem Cell Biology Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

3- Biotechnology Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

4- Tissue Engineering and Applied Cell Sciences Department, School of Advanced Medical Technologies, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

***Corresponding Author:**
Fatemeh Kuchakzade

Email:
fatemehkuchakzade@gmail.com

Received:
2026-01-29
Revised:
2026-05-21
Accepted:
2026-05-31

Volume:2
Issue no.1

Copyright © 2025 The Authors.
This work is licensed under a Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

AMD stands among the most common and severely disabling eye diseases worldwide, affecting millions of individuals each year. The condition involves progressive degeneration of the central retina known as the macula or yellow spot, leading to gradual loss of central vision that can ultimately result in blindness. AMD primarily affects people over 65 years old, with women experiencing slightly higher rates than men. Disease progression depends heavily on damage to the outer blood-retinal barrier, a critical structure composed of RPE, Bruch's membrane, and choroidal blood vessels that regulates nutrient and oxygen exchange while maintaining retinal physiological balance. AMD exists in two main forms: dry and wet. The dry form, which accounts for most cases, involves slow but steady breakdown of photoreceptor cells together with drusen deposits following a gradual yet persistent course. In contrast, wet AMD features growth of abnormal blood vessels and fluid leakage, causing more rapid and extensive damage to retinal cells. Conventional laboratory models including two-dimensional cell cultures and Transwell systems fail to adequately reproduce the retina's complex three-dimensional structure or accurately replicate long-term functional maturation and cell-cell interactions. 3D bioprinting emerges as an innovative technique capable of producing 3D constructs that closely resemble native retinal tissue. These models enable detailed examination of disease mechanisms, evaluation of cellular responses to various drugs, and development of personalized treatment strategies. This review provides comprehensive coverage of blood-retinal barrier physiology, 3D bioprinting techniques, modeling of both dry and wet AMD forms, pharmaceutical applications, and future directions in this field.

Keywords: Bruch's membrane, Choroidal neovascularization, Drusen deposits, Geographic atrophy, Induced pluripotent stem cells, Retinal pigment epithelium

How to cite this article:
Mofakhami por Mehrabadi, AR., Negahi, M., Haghiralsadat, BF., Kouchakzadeh, F. 3D printed in vitro models of the blood-retinal barrier to study AMD mechanisms. Regenerative Biomedicine, 2026; 2(1): 124-141. https://doi.org/10.22034/jrb.2026.07.V2I1A8

Introduction

Age-related macular degeneration (AMD) represents a serious eye disease that significantly impairs quality of life for millions of people around the world (1). Its frequency increases dramatically with age, affecting a substantial proportion of individuals over 80 years old. In addition to direct effects on vision, AMD creates significant economic and social burdens on healthcare systems through high treatment costs, long-term care requirements, and reduced workforce productivity (2). In many countries, the condition ranks as the leading cause of blindness and visual impairment among older adults (3). At the heart of AMD pathology lies dysfunction of the outer blood-retinal barrier, a fragile but critical structure essential for normal retinal function (4). This barrier consists of three main components: the retinal pigment epithelium (RPE) organized as a single layer of hexagonal cells, Bruch's membrane as a thin semi-permeable layer, and the choroidal vascular network responsible for blood and oxygen supply (4, 5). RPE cells perform multiple essential functions including absorption of excess light, formation of selective transport barriers for fluid movement, delivery of nutrients to photoreceptor cells, and removal of metabolic waste products (6). Bruch's membrane serves as a natural filter that permits passage of essential molecules while preventing accumulation of waste materials (7). In AMD, progressive dysfunction of the outer blood-retinal barrier gradually damages photoreceptor cells. The dry form features accumulation of extracellular deposits called drusen that disrupt nutrient exchange and structural integrity, leading to slow loss of RPE function and central vision (8, 9). This process can continue for years before resulting in geographic atrophy, defined as complete loss of RPE cells in specific areas (10). Wet AMD follows a different and more aggressive course (11). Chronic hypoxia and inflammation within the blood-retinal barrier stimulate production of vascular endothelial growth factor (VEGF), triggering growth of abnormal blood vessels beneath the retina (12). These fragile vessels readily leak blood and fluid, causing macular swelling and severe photoreceptor damage. Consequently, vision loss occurs much more rapidly and severely in wet AMD compared to the dry form (11). Although researchers have developed various animal models to study AMD, these models cannot fully capture the complex human-specific features of the disease (13). Traditional two-dimensional RPE cell cultures also demonstrate significant limitations, lacking the three-dimensional architecture and physiological environment of human retina, adequate functional maturation, and complex cell-cell and molecular interactions (14). Even advanced Transwell systems, despite making progress, fail to completely replicate blood-retinal barrier function (15). Three-dimensional bioprinting emerges as a revolutionary technology that enables creation of 3D models closely resembling native retinal tissue (16). These sophisticated constructs permit detailed investigation of disease mechanisms at the molecular level while providing optimal platforms for studying cellular interactions and testing new drug effectiveness (17). This technology promises to drive development of targeted, personalized AMD treatments and open important new directions in both preclinical and clinical research (Fig. 1) (18).

OPEN ACCESS

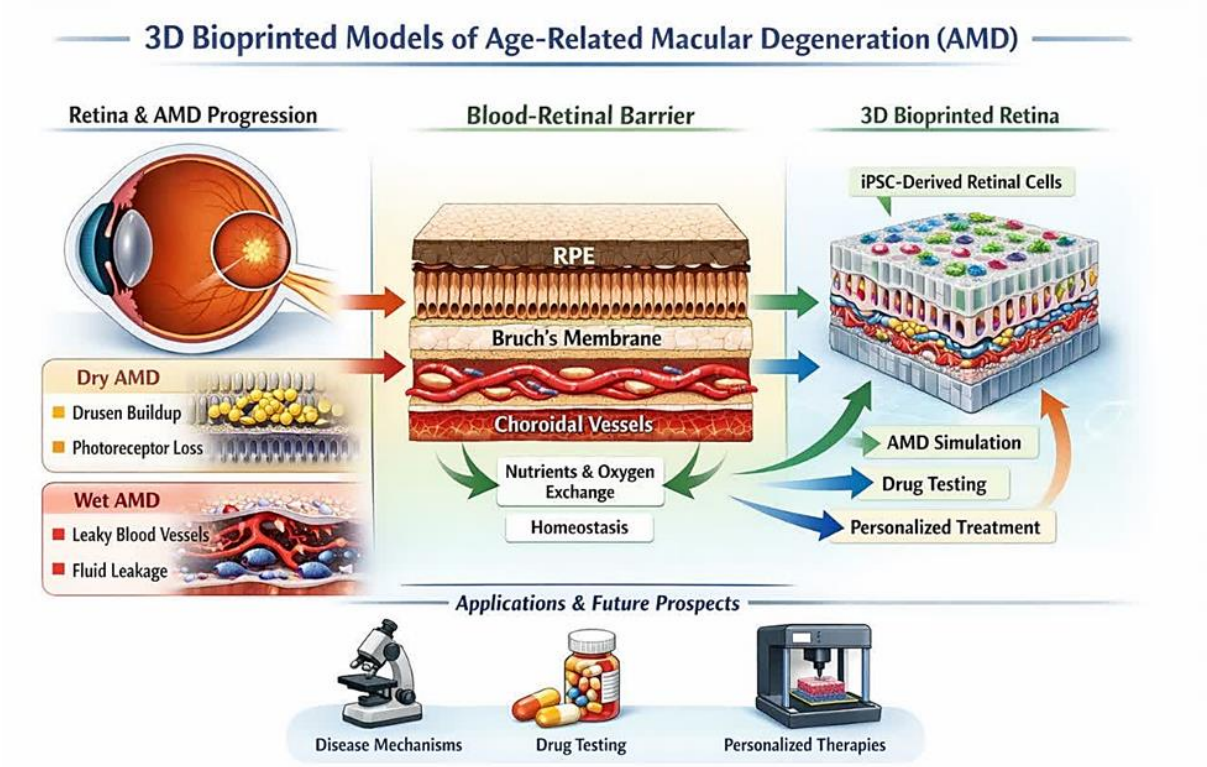

Figure 1. This graphical abstract illustrates three-dimensional bioprinted models developed specifically to investigate age-related macular degeneration (AMD), with particular focus on the essential role played by the blood-retinal barrier in disease onset and progression. The figure shows how carefully constructed layers (consisting of retinal pigment epithelium (RPE), Bruch's membrane, and choroidal blood vessels) accurately reproduce both anatomical structure and functional relationships, including nutrient transport together with the characteristic pathological features of dry AMD (drusen accumulation) and wet AMD (increased vascular permeability). Using retinal cells derived from induced pluripotent stem cells (iPSCs), these models create retina-like tissue constructs that reliably replicate AMD disease processes under in vitro conditions. The highlighted applications include clarifying disease mechanisms, accelerating drug testing, and developing customized treatment approaches matched to individual patient characteristics. Fundamentally, this innovative methodology connects laboratory research with clinical practice, providing a powerful platform for designing targeted therapies to prevent AMD-related vision loss.

Physiology of the Blood-Retinal Barrier and Pathophysiology of Age-Related Macular Degeneration

The blood-retinal barrier represents a highly specialized and essential physiological system divided into two distinct components: the inner blood-retinal barrier and the outer blood-retinal barrier (19). The inner barrier primarily consists of retinal endothelial cells supported by pericytes and astrocytes, which carefully regulate transport of glucose and essential nutrients into retinal tissue (20). This article focuses on the outer blood-retinal barrier, comprising the RPE and Bruch's membrane, which plays the dominant role in maintaining photoreceptor cell health and function (12). RPE cells form a monolayer of relatively large, hexagonal, flattened cells containing pigment-filled melanosomes that absorb excess light and prevent scatter within the retina (21). Tight junctions composed mainly of zonula occludens proteins and

https://doi.org/10.22034/jrb.2026.07.V2I1A8

occludin strictly limit molecular passage between cells (22). Sodium-potassium pumps actively control fluid and ion movement to maintain retinal fluid and electrolyte balance (23). RPE cells also produce and absorb important signaling molecules including pigment epithelium-derived factor (PEDF), which supports photoreceptor survival while inhibiting abnormal blood vessel growth (24). Autophagy processes in RPE cells systematically remove waste materials and dead cellular components, helping maintain retinal stability (25). Bruch's membrane appears as a thin, transparent, flexible layer situated between RPE cells and choroidal blood vessels (26). Organized into five distinct layers, this structure functions as a natural filter that allows passage of essential molecules such as oxygen and coenzyme Q10 while trapping cellular waste products (27). During age-related macular degeneration (AMD) progression, Bruch's membrane gradually thins and accumulates deposits. In dry AMD, lipid-rich deposits called drusen accumulate beneath RPE cells (28). These cholesterol- and protein-containing deposits resist complete cellular clearance. Drusen buildup blocks efficient oxygen and nutrient flow, creating localized hypoxic environments (23). This oxygen deprivation activates hypoxia-inducible factors, increases mitochondrial oxidative stress and reactive oxygen species production, and triggers programmed cell death pathways (29). The consequences include RPE cell loss, formation of large atrophic areas known as geographic atrophy, and progressive decline of central vision (30). Wet AMD involves faster and more destructive disease mechanisms. Hypoxia and inflammation in the outer blood-retinal barrier substantially increase vascular endothelial growth factor (VEGF) levels (31). Damaged RPE cells release VEGF to stimulate new blood vessel growth, but these abnormal vessels originating from the choroid beneath the retina prove weak and leaky, causing macular swelling and rapid photoreceptor cell destruction (32). Vision loss in wet AMD develops within weeks to months and proves more severe than dry AMD. The complement system plays a critical role in dry AMD pathology (33). Genetic variations in complement factor H cause abnormal complement activation and excessive inflammation that damage RPE cells (34). Activation of the NLRP3 inflammasome increases production of inflammatory cytokines such as interleukin-6, worsening cellular injury (35). Faithfully reproducing these complex processes in vitro requires advanced three-dimensional models capable of recreating oxygen gradients, hydrostatic pressure, and combined hypoxic-inflammatory conditions (36). Agents including lipopolysaccharide and cobalt chloride effectively induce inflammatory responses and oxygen deprivation (37). Three-dimensional bioprinted retinal models featuring precise layering of different cell types including RPE cells, endothelial cells, and supporting cells accurately replicate both normal human retinal physiology and pathological conditions, providing an ideal platform for investigating AMD disease mechanisms and testing potential therapies (14, 38).

History of Bioprinting in Blood-Retinal Barrier Tissue Engineering

Three-dimensional bioprinting ranks among the most advanced techniques in tissue

engineering, providing the ability to accurately recreate the complex layered structure of the blood-retinal barrier (39). The technology traces its origins to the 1980s, when researchers first proposed layer-by-layer fabrication methods for creating metal implants and prosthetics (40, 41). In 1986, Chuck Hull introduced the term 3D printing while developing equipment capable of producing plastic prototype models. The field advanced significantly during the early 2000s when scientists successfully printed living cells using specialized bioinks containing viable cellular components (42, 43). In ophthalmology, adoption of bioprinting accelerated after 2010 (44). Researchers created three-dimensional RPE models using stem cell sources that could replicate drusen formation and investigate AMD disease mechanisms (14). Subsequent developments produced more complex blood-retinal barrier constructs incorporating RPE cell layers, Bruch's membrane equivalents, and endothelial cells, achieving electrical resistance values similar to natural tissue (45). Recent progress focuses heavily on induced pluripotent stem cells (iPSCs) reprogrammed from patients' own skin fibroblasts, making possible the creation of personalized tissue models (46). Bioprinted blood-retinal barrier models excel at accurately simulating drusen deposits and natural fluid flow patterns, providing precise research tools for AMD studies and patient-specific treatment development (14). The history of bioprinting demonstrates its evolution from simple proof-of-concept structures to sophisticated constructs that closely resemble living tissue, opening important new pathways for AMD therapeutic research (39). Several landmark three-dimensional bioprinted models of the outer blood-retinal barrier (BRB) and retinal tissue have been specifically designed for AMD research, confirming the feasibility of recreating native tissue architecture and disease characteristics using in vitro systems.

Technical Methods of 3D Bioprinting for the Blood-Retinal Barrier

Building a functional blood-retinal barrier starting from individual cells presents major bioengineering challenges (47). Three-dimensional bioprinting has emerged as one of the most promising techniques available to researchers for overcoming these difficulties (48). The approach relies on precise layer-by-layer deposition of cells, biomaterials, and bioactive molecules to recreate the complex structure of the outer retina (49). For studies focused specifically on age-related macular degeneration, accurate reconstruction requires precise positioning of retinal pigment epithelium layers, Bruch's membrane equivalents, and choroidal blood vessels in their exact anatomical relationships, essential for achieving native tissue-like behavior (49, 50). Current researchers utilize three main bioprinting methods, each offering distinct advantages and limitations regarding printing resolution, cell survival during fabrication, and complexity of achievable structures (39). 1) Extrusion-based bioprinting provides the most straightforward technical approach (40). Cell-containing bioinks move through nozzles using either pneumatic pressure or mechanical pistons, creating structures through successive layer deposition (51). When constructing blood-retinal barrier models, the process typically begins by

https://doi.org/10.22034/jrb.2026.07.V2I1A8

printing a base layer that mimics Bruch's membrane, where materials like collagen, gelatin methacrylate, or similar supportive hydrogels work well (49, 52). Retinal pigment epithelial cells then form a single cell layer on this foundation, followed by endothelial cells and perivascular cells representing choroidal microvasculature (53). Optimal printing conditions include speeds of 5-10 mm/s with nozzle diameters between 150-250 μm, which provide sufficient resolution to reproduce major tissue layers while preserving adequate cell viability (54-56). Importantly, extrusion pressure represents the main factor causing cell damage rather than nozzle size, as higher pressures create exponentially increasing shear forces that reduce cell survival (57). Conical nozzles generally perform better than cylindrical ones because they require lower pressure to achieve the same flow speed, thereby minimizing cell injury (58). 2) Inkjet bioprinting operates on a completely different principle (59). Instead of continuous extrusion, piezoelectric or thermal mechanisms eject tiny droplets (picoliter volumes) of low-viscosity bioinks with excellent control (60). This method proves particularly effective for precisely arranging delicate cell types (like induced pluripotent stem cell-derived retinal pigment epithelium or microvascular endothelial cells) into thin layers or gradients that match the polarized organization characteristic of the outer blood-retinal barrier (36, 39). Resolution reaches tens of micrometers, allowing exact placement not only of cells but also growth factors and extracellular matrix components (61). This level of control becomes especially valuable when directing barrier formation or studying neovascularization processes relevant to AMD pathology (14). Studies confirm inkjet bioprinting achieves cell viability above 85% with bioink viscosities ranging from 3 to 30 mPa·s (62). However, challenges including cell settling in printheads and limited maximum cell concentrations remain significant limitations (47). 3) Laser-assisted bioprinting follows a different technical path (59). Rather than forcing material through nozzles, focused laser pulses transfer small volumes of bioink from a donor slide to a receiving surface (63). The primary advantage lies in eliminating direct nozzle contact, which dramatically reduces mechanical stress on cells during printing (40). Cell survival routinely exceeds 90%, making this method ideal for sensitive retinal cells that cannot withstand more aggressive processing (39, 64). The technique also creates sharp, clean boundaries between retinal pigment epithelium and vascular layers, a challenge for other methods (63). High spatial precision offers significant benefits when creating Bruch's membrane-like sheets and microvascular networks that must closely mimic native outer blood-retinal barrier anatomy (65, 66). Research demonstrates successful fabrication of layered corneal tissues using human embryonic stem cell-derived limbal epithelial cells and adipose-derived stem cells, showing excellent post-printing survival and proper tissue organization (62). Successful printing represents only part of the complete process. After assembly, constructs require carefully controlled culture conditions to achieve full functional maturity (67). Static culture dishes frequently prove inadequate for these complex tissues, so researchers increasingly use bioreactors and perfusion systems (68). These systems generate physiologically relevant fluid shear stress, improve oxygen

and nutrient delivery throughout the construct, and support long-term retinal cell culture in ways static conditions cannot achieve (64). Rotating wall vessel bioreactors accelerate organoid growth and improve neuronal differentiation compared to standard suspension culture (69). Continuous monitoring of barrier function through transepithelial electrical resistance measurements integrated with perfusion systems provides real-time data about tissue development (36, 70).

Materials and Scaffolds Used in Bioprinted Blood–Retina Barrier Models

Scaffolds form the essential structural foundation for bioprinted blood-retina barrier (BRB) models and must simultaneously provide biocompatibility, appropriate porosity, and controlled biodegradability (71). Hydrogels represent the most widely used materials for these applications because they contain more than 90% water, closely resembling the natural hydrated environment of living tissues (72). The most commonly utilized hydrogels include methacrylated gelatin, valued for its optical clarity and ability to maintain stable connections between adjacent cells (73); chitosan, a natural polysaccharide derived from chitin that offers antimicrobial properties suitable for creating Bruch's membrane layers (74); polycaprolactone, a synthetic polymer providing high mechanical strength together with slow and predictable degradation; silk fibroin, a natural protein with excellent tensile properties and low permeability to large molecules (71); and alginate, a seaweed-derived polysaccharide that forms stable gels through calcium-mediated crosslinking while supporting high cell survival rates (75, 76). Advanced composite scaffolds, such as combinations of polycaprolactone and chitosan, successfully combine mechanical durability with biological functionality (77). The cellular components incorporated into these scaffold systems include RPE cells generated from patient-specific induced pluripotent stem cells (iPSCs), human umbilical vein endothelial cells (HUVECs) to replicate choroidal blood vessels, and fibroblasts (78). Adipose tissue-derived mesenchymal stem cells serve as an additional cell source capable of differentiating into RPE-like cells (79). Bioinks also contain carefully selected growth factors to guide cell development and ensure proper functional maturation, particularly pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) (80). Bone morphogenetic protein-2 (BMP-2) nanoparticles embedded within chitosan-collagen hydrogel systems provide controlled and sustained release of this important signaling molecule (81). Recent developments include three-dimensional porous scaffolds with integrated orthogonal channel networks designed to enhance mechanical stability when combined with softer gelatin-based layers (82). These engineered scaffolds, populated with adipose-derived stem cells, demonstrate strong potential for promoting blood vessel formation (83). Despite these significant advances, important challenges persist, including the need to maintain high cell viability throughout the bioprinting process and the difficulty of scaling constructs to sizes relevant for human applications (84). However, experimental results consistently

https://doi.org/10.22034/jrb.2026.07.V2I1A8

demonstrate that current bioprinting technologies rapidly approach the capability to create fully functional BRB models (82).

Simulation of Dry and Wet Age-Related Macular Degeneration in Bioprinted Models

Dry Age-Related Macular Degeneration Simulation

Dry AMD represents approximately 90% of all cases and features drusen accumulation, RPE atrophy, and progressive photoreceptor cell loss (85). Although this form advances more slowly than wet AMD, it steadily impairs central vision and diminishes quality of life (86). Three-dimensional bioprinted models accurately reproduce the cellular and molecular features of dry AMD by recreating the native blood-retina barrier (BRB) structure while maintaining complex interactions between RPE cells, choroidal blood vessels, and supporting stromal cells (14). Researchers at the National Eye Institute have developed bioprinted constructs containing fibroblasts, pericytes, vascular endothelial cells, and RPE cells (14, 87). When printed in thermosensitive hydrogels, these cellular components develop into mature, densely packed networks over 42 days of culture (88). Drusen formation occurs through addition of oxidized cholesterol or low-density lipoproteins to the culture medium, creating deposits beneath the RPE layer that increase Bruch's membrane thickness in patterns matching patient tissue pathology (89). Drusen accumulation disrupts RPE autophagy (the essential process that recycles damaged proteins and cellular components) leading to oxidative stress buildup (90). Measurements of reactive oxygen species demonstrate a threefold increase in these stressed model systems (91). This oxidative damage activates hypoxia-inducible factor-1α and initiates programmed cell death pathways. Geographic atrophy, the advanced stage of dry AMD, involves complete loss of RPE cells across large areas (92, 93). In bioprinted models, hypoxia induced by cobalt chloride treatment produces regions devoid of RPE cells, accompanied by transepithelial electrical resistance dropping from approximately 200 $\Omega \cdot cm^2$ to less than 50 $\Omega \cdot cm^2$, indicating pathological fluid leakage (14). Optical and electron microscopy confirm thinning of Bruch's membrane, infiltration of inflammatory cells, and structural damage to RPE cells (90). Three-dimensional bioprinting reveals specific spatial and temporal relationships between drusen formation, impaired RPE autophagy, and complement system dysfunction that remain undetectable in conventional flat 2D cultures (14, 63). Time-course imaging shows that lipid deposits resembling drusen begin accumulating beneath the RPE layer within two to three weeks (94). As these deposits thicken, they expand the Bruch's membrane layers and interfere with nutrient delivery to photoreceptor cells (14). This creates localized regions of low oxygen that can be confirmed through elevated hypoxia-inducible factor-1α expression and pimonidazole staining (95). These hypoxic conditions then activate NLRP3 inflammasomes precisely at the deposit-RPE interface, generating concentrated zones of IL-6 and IL-1β production (14, 96). These cytokines create a destructive feedback loop that amplifies oxidative stress through complement system activation (97). Quantification of autophagic flux in these 3D

models demonstrates that oxidative stress-induced lysosomal dysfunction reduces clearance rates by 50-70%, causing buildup of undigested cellular waste products (98). Confocal microscopy reveals accumulation of ubiquitinated protein aggregates and fragmented mitochondria (63). Importantly from a therapeutic perspective, application of complement inhibitors to the basal side of these bioprinted constructs reduces C3 deposition and restores autophagic function (14). This suggests opportunities for early intervention in dry AMD by blocking harmful interactions between complement proteins and RPE cells (99). Beyond completely bioprinted constructs, hybrid approaches combining 3D bioprinting with prefabricated biomimetic membranes show increasing promise (18). These methods improve structural accuracy of the outer blood-retina barrier (100). Nanofibrous or microporous polymer membranes serve as Bruch's membrane substitutes that researchers then seed or overlay with bioprinted RPE and endothelial cells. This combination maintains barrier properties over extended culture periods while still permitting natural formation of drusen-like deposits. These hybrid 3D systems provide robust platforms for testing potential treatments including antioxidants and complement pathway inhibitors, while also enabling direct comparisons with traditional 2D cultures across measures of RPE function, barrier integrity, and inflammatory responses (14, 59, 101).

Wet Age-Related Macular Degeneration Simulation

Wet AMD presents with choroidal neovascularization and fluid leakage, accounting for about 10% of all cases (102). This form progresses rapidly and demands immediate treatment intervention (103). Models developed by the National Eye Institute recreate wet AMD by adding 50 ng/mL VEGF to the vascular layer, which stimulates endothelial cell sprouting from the choroid toward the RPE (14). The newly formed blood vessels have incomplete walls that permit leakage of tracer molecules such as fluorescein-dextran. Macular edema simulation occurs through approximately 30% thickening of the RPE layer (14, 104). Initial hypoxia created by treatment with 200 μM cobalt chloride triggers VEGF production. Pericytes and endothelial cells printed in thermosensitive hydrogels form a dense capillary network within nine days (105). RPE cells are then seeded and mature over one month, establishing a functional BRB that supports exchange of cellular signals including pigment epithelium-derived factor (PEDF) (106). Anti-VEGF drugs such as ranibizumab effectively suppress abnormal blood vessel growth and restore normal tissue structure (107). Optimal cell ratios of 1:2:3 (pericytes:endothelial cells:fibroblasts) ensure formation of dense microvascular networks (106). The three-dimensional structure of bioprinted models provides researchers with precise control over VEGF gradients that cannot be achieved with traditional 2D cultures, gradients that directly drive choroidal neovascularization (39). Researchers create specific oxygen gradients using glucose oxidase or controlled perfusion systems to generate different hypoxic conditions in the choroidal layers (14). Physiological hypoxia levels range from 5-10% O_2, while pathological hypoxia drops to 1-3% O_2. This difference determines both

https://doi.org/10.22034/jrb.2026.07.V2I1A8

the amount of VEGF secreted by RPE cells and its precise location (108).

Live-cell imaging reveals that pathological VEGF levels above 40 ng/mL trigger choroidal microvessel sprouting toward RPE within 5-7 days, while controlled levels below 20 ng/mL produce normal vascular remodeling without chaotic growth (109).

A key finding that demonstrates the value of these models for drug development concerns the direction of anti-VEGF drug delivery: perfusion from the apical RPE-facing side versus the basal choroid-facing side produces dramatically different penetration patterns (110).

Despite intact tight junctions, only 15-20% of ranibizumab reaches the basal compartment (109).

This insight explains why bioprinted BRB models prove so valuable, they enable optimization of drug delivery strategies specifically targeting choroidal neovascularization (CNV) lesions (36). Together, these 3D wet AMD models create controllable experimental platforms (63). Researchers can dissect the complex interactions between hypoxia, VEGF-driven neovascularization, and inflammatory factors like interleukin-6 with precision (36, 63).

The experimental flexibility is substantial: by adjusting cell composition, growth factor concentrations, and culture conditions, investigators can recreate all the hallmark features of neovascular AMD, leaky microvessels, edema-like thickening, and progressive RPE breakdown (111).

This level of experimental control enables rational testing of anti-VEGF agents and combination therapies, moving beyond uncertain 2D predictions toward clinically relevant outcomes (48, 99).

Evaluation and Validation of Bioprinted Models

Evaluation of bioprinted blood-retinal barrier models requires a comprehensive approach that carefully examines structural, functional, and molecular characteristics to confirm they accurately replicate the physiology of native retinal tissue (15). At the functional level, barrier integrity represents the primary measure through transepithelial electrical resistance measurements, where values exceeding 200 $\Omega \cdot cm^2$ demonstrate successful formation of tight junctions between adjacent cells (112, 113). These findings receive further support from permeability assays showing less than 0.5% passage of 4-70 kDa fluorescent dextran tracers per hour, which confirms both electrical resistance and selective permeability properties essential for normal barrier function as well as disease-related dysfunction in retinal conditions (112). Molecular characterization proceeds through immunofluorescence analysis of key protein markers, including zonula occludens-1 and occludin proteins that localize specifically to tight junction sites to verify barrier formation (114), pigment epithelium-derived factor produced exclusively by retinal pigment epithelial cells to confirm appropriate cellular identity (115), and von Willebrand factor detected within choroidal blood vessels to validate endothelial cell differentiation (116). RNA sequencing analysis provides additional evidence that these engineered constructs display gene expression profiles closely matching those found in native retinal tissue, offering molecular confirmation of their physiological accuracy (14). For disease modeling applications, these constructs undergo

rigorous testing against established clinical pathology standards (117), where lipid-rich drusen deposits characteristic of dry AMD become identifiable through Oil Red O staining (89, 118), geographic atrophy appears through assessment of pigment loss indicating retinal pigment epithelial cell degeneration (119), and abnormal vascular leakage typical of wet AMD becomes visible through fluorescein angiography confirming neovascularization patterns (120). The ability to perform long-term monitoring for up to 60 days allows researchers to track disease progression patterns and therapeutic responses across biologically relevant time periods (121), which proves particularly useful for investigating slowly progressive conditions like dry AMD while also evaluating the sustained effectiveness and safety profiles of potential treatment interventions (122).

Pharmaceutical Applications of Bioprinted Blood–Retina Barrier Models

Bioprinted blood-retinal barrier models serve as essential platforms for preclinical drug screening in AMD (123), offering accurate representation of the outer retina's three-dimensional structure, cell-to-cell interactions, and barrier functions that two-dimensional cultures cannot reproduce (47). In 3D-printed models of wet AMD, researchers can deliver anti-angiogenic agents directly to vascular compartments and systematically assess their effectiveness across multiple parameters (52, 78), including their ability to suppress abnormal endothelial growth (64), reduce vascular leakage (48), and promote recovery of normal RPE cell morphology (124). Specific measurements provide concrete data for evaluation, such as microvessel density counts, quantification of fluorescent tracer leakage, and transepithelial electrical resistance (TEER) values that indicate barrier integrity (15, 125). For dry AMD models, these 3D-printed constructs enable testing of candidate drugs targeting different disease mechanisms, including oxidative stress pathways (90), autophagy impairment (126), and complement system activation (126). Long-term culture monitoring examines whether drusen-like deposits form or diminish (47), tracks RPE cell survival versus cell death, evaluates mitochondrial health versus damage, and measures changes in inflammatory gene expression over time (127, 128). These controlled in vitro systems allow researchers to optimize dosing schedules and drug combinations before advancing to animal studies or clinical trials (129). A major advance comes from incorporating patient-specific induced pluripotent stem cells into these 3D blood-retina barrier (BRB) models (130). Using cells that carry each patient's unique genetic profile, researchers can investigate how specific genetic risk factors influence drug responses and disease progression (99). This approach facilitates evaluation of natural compounds, small molecule drugs, and gene therapy vectors (whether embedded directly in the tissue or delivered across the barrier) to determine their permeability, effectiveness, and potential safety issues in conditions resembling human physiology (44). Beyond the drugs themselves, these models provide testing platforms for advanced drug delivery systems (40). Long-acting implants and nanoparticle carriers can be thoroughly evaluated to optimize their release profiles

https://doi.org/10.22034/jrb.2026.07.V2I1A8

and targeting specifically to the RPE-choroid interface (131). Collectively, these capabilities accelerate development of treatment strategies customized to individual patients, advancing AMD therapy from generic approaches toward true personalized medicine (132).

Advantages and Limitations of Bioprinted Models

BRB models offer several key advantages, including accurate replication of native 3D tissue structure, establishment of oxygen and nutrient gradients, support for complex cell-cell interactions, and long-term evaluation of cellular processes (39). These models enable detailed investigation of AMD mechanisms such as oxidative stress, apoptosis, autophagy, and neovascularization (133). Additionally, the use of patient-derived cells with diverse genetic backgrounds provides a platform for developing personalized therapies and predicting individual treatment responses (134). However, important limitations remain. Maintaining cell viability during and after bioprinting remains challenging (64). Scaling these models to human-relevant sizes for clinical applications is currently limited (135). The full physiological complexity of vascular networks and their interactions with other retinal cells (neurons, microglia) has not been completely recapitulated (14). Furthermore, high production costs and the need for specialized equipment, including precision bioprinters and bioreactors, present practical barriers to widespread adoption (136).

Future Perspectives

Advances in bioprinting technology will BRB models to more closely resemble native human tissue (36). Integration with emerging technologies such as microfluidics, nanotechnology, biosensors, and artificial intelligence will allow precise control of physiological conditions and simulation of complex disease states (137, 138). Smart bioactive scaffolds capable of controlled release of growth factors and anti-inflammatory drugs will facilitate targeted, patient-specific treatments (139). Over the next decade, bioprinted BRB models are expected to play central roles in preclinical and potentially clinical studies (36). They may reduce reliance on animal testing, accelerating new drug development (140). Patient-specific cells modeling unique genetic and environmental factors will enable personalized therapeutic approaches and accurate prediction of treatment responses (40, 141).

Conclusion

Three-dimensional bioprinting of the blood-retina barrier represents a powerful tool for studying age-related macular degeneration. These models accurately replicate cellular and molecular disease processes, providing platforms for drug screening, cell therapy, and gene therapy development. Recent advances in stem cells, biomaterials, and bioprinting technology have opened new opportunities for personalized AMD treatment. Integration of these approaches with innovative pharmacological and biotechnological strategies promises substantial progress in managing this debilitating disease.

Authors' contributions

All authors contributed to the investigation, conceptualization, and analysis of the

information in this manuscript, and were involved in the writing process.

Funding

This study was not funded by any funding institute.

Availability of data and materials

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

Table 1. Abbreviations

AMD	Age-related Macular Degeneration
BRB	**Blood-Retinal Barrier**
oBRB	**Outer Blood-Retinal Barrier**
iBRB	**Inner Blood-Retinal Barrier**
RPE	**Retinal Pigment Epithelium**
VEGF	**Vascular Endothelial Growth Factor**
PEDF	**Pigment Epithelium-Derived Factor**
TEER	**Transepithelial Electrical Resistance**
iPSCs	**Induced Pluripotent Stem Cells**
HUVECs	**Human Umbilical Vein Endothelial Cells**
CNV	**Choroidal Neovascularization**
ROS	**Reactive Oxygen Species**
HIF-1α	**Hypoxia-Inducible Factor-1 Alpha**
NLRP3	**NOD-, LRR- and Pyrin Domain-Containing Protein 3**
IL-6	**Interleukin-6**
CFH	**Complement Factor H**
ZO-1	**Zonula Occludens-1**
vWF	**von Willebrand Factor**
RNA-seq	**RNA Sequencing**
3D	**Three-Dimensional**
PCL	**Polycaprolactone**
BMP-2	**Bone Morphogenetic Protein-2**
LPS	**Lipopolysaccharide**
CoQ10	**Coenzyme Q10**
ECM	**Extracellular Matrix**
BBB	**Blood-Brain Barrier**
DME	**Diabetic Macular Edema**
DR	**Diabetic Retinopathy**

Acknowledgements

The authors would like to acknowledge the assistance of ChatGPT (OpenAI) in the visualization and design of Figure 1.

References

1. Fleckenstein M, Schmitz-Valckenberg S, Chakravarthy U. Age-related macular degeneration: a review. Jama. 2024;331(2):147-57.

2. Wichrowska M, Goździewska E, Kocięcki J. The safety of Anti-VEGF treatment, in the context of the retinal nerve Fibre Layer, in patients with wet age-related Macular Degeneration: a review. Frontiers in Bioscience-Landmark. 2023;28(9):222.

3. Ruan Y, Jiang S, Gericke A. Age-related macular degeneration: role of oxidative stress and blood vessels. International journal of molecular sciences. 2021;22(3):1296.

4. Martins B, Pires M, Ambrósio AF, Girão H, Fernandes R. Contribution of extracellular vesicles for the pathogenesis of retinal diseases: shedding light on blood-retinal barrier dysfunction. Journal of biomedical science. 2024;31(1):48.

5. Ashraf R, Hussain I, Shafi T, Malik SH, Qadir S. Exosomal Biomarkers and Extracellular Vesicles in Diabetic Retinopathy: Emerging Mechanisms, Diagnostic Signatures and Therapeutic Frontiers. Pan-African Journal of Health and Psychological Sciences. 2026;2(1).

6. Bhattacharyya A. The detrimental effects of progression of retinal degeneration in the visual cortex. Frontiers in Cellular Neuroscience. 2022;16:904175.

7. de Guimaraes TAC, Varela MD, Georgiou M, Michaelides M. Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. British Journal of Ophthalmology. 2022;106(3):297-304.

8. O'Leary F, MB B. The inner blood retinal barrier in ocular disease and circadian regulation: its role in age related macular degeneration development and other neuro-ophthalmology disorders. 2022.

https://doi.org/10.22034/jrb.2026.07.V2I1A8

9. Bora K, Kushwah N, Maurya M, Pavlovich MC, Wang Z, Chen J. Assessment of inner blood–retinal barrier: Animal models and methods. Cells. 2023;12(20):2443.

10. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. Geographic atrophy: mechanism of disease, pathophysiology, and role of the complement system. Journal of Managed Care & Specialty Pharmacy. 2023;29(5-a Suppl):S2-S11.
11. Marchesi N, Capierri M, Pascale A, Barbieri A. Different therapeutic approaches for dry and wet AMD. International Journal of Molecular Sciences. 2024;25(23):13053.

12. Hang Z, Li Y, Ren W, Du H. The blood–retinal barrier in ocular pathologies: an updated narrative review. International Ophthalmology. 2025;46(1):10.

13. Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nature Reviews Genetics. 2022;23(8):467-91.

14. Song MJ, Quinn R, Nguyen E, Hampton C, Sharma R, Park TS, et al. Bioprinted 3D outer retina barrier uncovers RPE-dependent choroidal phenotype in advanced macular degeneration. Nature Methods. 2023;20(1):149-61.

15. Apostolidi A, Stergiopoulos G, Bellou S, Markou M, Fotsis T, Murphy C, et al. Advances in Modeling the Inner Blood–Retinal Barrier: From Static Tissue Cell Cultures to Microphysiological Systems. Pharmaceuticals. 2025;18(9):1374.

16. Mirsky NA, Ehlen QT, Greenfield JA, Antonietti M, Slavin BV, Nayak VV, et al. Three-dimensional bioprinting: a comprehensive review for applications in tissue engineering and regenerative medicine. Bioengineering. 2024;11(8):777.

17. Neufeld L, Yeini E, Pozzi S, Satchi-Fainaro R. 3D bioprinted cancer models: from basic biology to drug development. Nature reviews Cancer. 2022;22(12):679-92.

18. Mina M, Goel AK, Mina F, Goubran D, Goel N. Three-Dimensional Printing for Accessible and Personalized Ophthalmic Care: A Review. Journal of Clinical & Translational Ophthalmology. 2025;3(2):6.

19. Zhang C-L, Ma J-J, Li X, Yan H-Q, Gui Y-K, Yan Z-X, et al. The role of transcytosis in the blood-retina barrier: from pathophysiological functions to drug delivery. Frontiers in Pharmacology. 2025;16:1565382.

20. Shah W, Gong Y, Qiao X, Lu Y, Ding Y, Zhang Z, et al. Exploring Endothelial Cell Dysfunction's Impact on the Brain-Retina Microenvironment Connection: Molecular Mechanisms and Implications. Molecular Neurobiology. 2025;62(6):7484-505.

21. Dontsov A, Ostrovsky M. Retinal pigment epithelium pigment granules: Norms, age relations and pathology. International Journal of Molecular Sciences. 2024;25(7):3609.

22. O'Leary F, Campbell M. The blood–retina barrier in health and disease. The FEBS journal. 2023;290(4):878-91.

23. Gabrielle Ph. Lipid metabolism and retinal diseases: Wiley Online Library; 2022.

24. Rickman CB, Strauss O. The Function of the Retinal Pigment Epithelium. Adler's Physiology of the Eye E-Book. 2024:339.

25. Gurubaran IS. Mitochondrial damage and clearance in retinal pigment epithelial cells: Wiley Online Library; 2024.
26. Askari S, Eskandari M. Advancements in Retina Bruch's Membrane on Chip: A Bibliometric Review. Regenerative Engineering and Translational Medicine. 2025:1-15.

27.Markitantova Y, Simirskii V. Endogenous and exogenous regulation of redox homeostasis in retinal pigment epithelium cells: an updated antioxidant perspective. International Journal of Molecular Sciences. 2023;24(13):10776.

28. Chen L, Yang P, Curcio CA. Visualizing lipid behind the retina in aging and age-related macular degeneration, via indocyanine green angiography (ASHS-LIA). Eye. 2022;36(9):1735-46.

29. Zhang S-M, Fan B, Li Y-L, Zuo Z-Y, Li G-Y. Oxidative stress-involved mitophagy of retinal pigment epithelium and retinal degenerative diseases. Cellular and Molecular Neurobiology. 2023;43(7):3265-76.

30. Vujosevic S, Alovisi C, Chakravarthy U. Epidemiology of geographic atrophy and its precursor features of intermediate age-related macular degeneration. Acta Ophthalmologica. 2023;101(8):839-56.

31. Srejovic JV, Muric MD, Jakovljevic VL, Srejovic IM, Sreckovic SB, Petrovic NT, et al. Molecular and cellular mechanisms involved in the pathophysiology of retinal vascular disease—interplay between inflammation and oxidative stress. International Journal of Molecular Sciences. 2024;25(21):11850.

32. Heloterä H, Kaarniranta K. A linkage between angiogenesis and inflammation in neovascular age-related macular degeneration. Cells. 2022;11(21):3453.

33. Piri N, Kaplan HJ. Role of complement in the onset of age-related macular degeneration. Biomolecules. 2023;13(5):832.

34. Armento A, Merle DA, Ueffing M. The noncanonical role of complement factor H in retinal pigment epithelium (RPE) cells and implications for age-related macular degeneration (AMD). Retinal Degenerative Diseases XIX: Mechanisms and Experimental Therapy: Springer; 2023. p. 9-13.

35. Shafi A, Akmal M, Sethi A, Chauhdary Z. A mechanistic insight of neuro-inflammation signaling pathways and implication in neurodegenerative disorders. Inflammopharmacology. 2025:1-10.

36. Yan R, Wang Y, Wang Y, Pang M, Wei L, Zhu M, et al. Bioengineering Approaches for the 3D Blood–Retinal Barrier: Disease Modeling and Drug Development. ACS Biomaterials Science & Engineering. 2025;11(10):5740-55.

37. Chen T-E, Lo J, Huang S-P, Chang K-C, Liu P-L, Wu H-E, et al. Glaucine inhibits hypoxia-induced

angiogenesis and attenuates LPS-induced inflammation in human retinal pigment epithelial ARPE-19 cells. European Journal of Pharmacology. 2024;981:176883.

38. Song MJ, Bharti K. 3D vascularized eye tissue models age-related macular degeneration. NATURE PORTFOLIO HEIDELBERGER PLATZ 3, BERLIN, 14197, GERMANY; 2023. p. 46-7.
39. Wu KY, Osman R, Kearn N, Kalevar A. Three-dimensional bioprinting for retinal tissue engineering. Biomimetics. 2024;9(12):733.

40. Wu KY, Tabari A, Mazerolle É, Tran SD. Towards precision ophthalmology: the role of 3D printing and bioprinting in oculoplastic surgery, retinal, corneal, and glaucoma treatment. Biomimetics. 2024;9(3):145.

41. Pandey G, Kolipaka T, Phatale V, Khairnar P, Abraham N, Shah S, et al. Exploring the potential of nano-biomaterials in tissue engineering. Biomaterial-Inspired Nanomedicines for Targeted Therapies: Springer; 2024. p. 31-54.

42. Jose RR, Rodriguez MJ, Dixon TA, Omenetto F, Kaplan DL. Evolution of bioinks and additive manufacturing technologies for 3D bioprinting. ACS biomaterials science & engineering. 2016;2(10):1662-78.

43. Thayer P, Martinez H, Gatenholm E. History and trends of 3D bioprinting. 3D Bioprinting: Principles and Protocols: Springer; 2020. p. 3-18.

44. Kim H, Ngo G-H, Hong W, Lee SH, Mahajan VB, DeBoer C. 3D bioprinting of cellular therapeutic systems in ophthalmology: from bioengineered tissue to personalized drug delivery. Current Ophthalmology Reports. 2025;13(1):10.

45. Marchand M, Nguyen BH, Tran SD. Advances in Regenerative Medicine, Cell Therapy, and 3D Bioprinting. Cell Biology and Translational Medicine, Volume 25: Advances in Regenerative Medicine and Cellular Therapy. 2025:115.

46. Liang S, Su Y, Yao R. 3D Bioprinting of Induced Pluripotent Stem Cells and Disease Modeling. Human iPSC-derived Disease Models for Drug Discovery: Springer; 2023. p. 29-56.

47. CORONINI G. A review of retinal tissue engineering and the possible application of dECM bioink in retinal 3D printing. 2018.

48. Choe S, Ye J, Zhang T, Gao J. Advanced Drug Delivery Systems for Age-Related Macular Degeneration Treatment: Latest Trends and Future Prospects. Advanced Healthcare Materials. 2025:e03757.

49. Molins B, Rodríguez A, Llorenç V, Adán A. Biomaterial engineering strategies for modeling the Bruch's membrane in age-related macular degeneration. Neural Regeneration Research. 2024;19(12):2626-36.

50. Ong J, Selvam A, Driban M, Zarnegar A, Da SIMMA, Joy J, et al. Characterizing Bruch's membrane: State-of-the-art imaging, computational segmentation, and biologic models in retinal disease and health. Progress in Retinal and Eye Research. 2025:101358.

51. Manzoli S, Merotto E, Piccoli M, Gobbo P, Todros S, Pavan PG. An Overview of 3D Bioprinting Impact on Cell Viability: From Damage Assessment to Protection Solutions. Journal of Functional Biomaterials. 2025;16(12):436.

52. Zhang C, Wang J, Wu H, Fan W, Li S, Wei D, et al. Hydrogel-based therapy for age-related macular degeneration: Current innovations, impediments, and future perspectives. Gels. 2024;10(3):158.
53. Wu A, Lu R, Lee E. Tissue engineering in age-related macular degeneration: A mini-review. Journal of Biological Engineering. 2022;16(1):11.

54.Lin N, Gagnon M, Wu KY. The third dimension of eye care: A comprehensive review of 3D printing in ophthalmology. Hardware. 2024;2(1):1-32.

55. Mohd N, Razali M, Ghazali MJ, Abu Kasim NH. Current advances of three-dimensional bioprinting application in dentistry: a scoping review. Materials. 2022;15(18):6398.

56. Arias-Peregrino VM, Tenorio-Barajas AY, Mendoza-Barrera CO, Román-Doval J, Lavariega-Sumano EF, Torres-Arellanes SP, et al. 3D printing for tissue engineering: printing techniques, biomaterials, challenges, and the emerging role of 4D bioprinting. Bioengineering. 2025;12(9):936.

57. Ruffini A. Fluid Mechanics in Ophthalmology: Age-Related Macular Degeneration from Pathogenesis to Treatment. 2024.

58. López-Varela E, Vidal PL, Pascual NO, Novo J, Ortega M. Fully-automatic 3D intuitive visualization of age-related macular degeneration fluid accumulations in OCT cubes. Journal of Digital Imaging. 2022;35(5):1271-82.

59. Ruiz-Alonso S, Villate-Beitia I, Gallego I, Lafuente-Merchan M, Puras G, Saenz-del-Burgo L, et al. Current insights into 3D bioprinting: An advanced approach for eye tissue regeneration. Pharmaceutics. 2021;13(3):308.

60. Hu G, Cebrero KG, Venkataraman N, Ravichandran D, Lin Y, Jin Z, et al. Tuning collagen and collagen-alginate mechanics through extrusion bioprinting process parameters. RSC advances. 2025;15(54):46591-601.

61. Ng WL, Shkolnikov V. Optimizing cell deposition for inkjet-based bioprinting. International Journal of Bioprinting. 2024.

62. Xu H-Q, Liu J-C, Zhang Z-Y, Xu C-X. A review on cell damage, viability, and functionality during 3D bioprinting. Military Medical Research. 2022;9(1):70.

63. Quinn RL. MACROPHAGE-INDUCED CHOROIDAL SENESCENCE TRIGGERS AGE-RELATED MACULAR DEGENERATION IN A 3D-BIOPRINTED HUMAN EYE TISSUE AND IN IRF5 KNOCKOUT MOUSE: Johns Hopkins University; 2022.

64. Wang Y, Jiang D, Wang Q, Cao Y, Guo H, Lu Y, et al. Three-dimensional tissue engineering and organoid technologies for retinal regeneration and therapy. Bioengineering & Translational Medicine. 2025;10(6):e70051.

https://doi.org/10.22034/jrb.2026.07.V2I1A8

65. Tan EYS. Biofabrication of choroid-retina tissue construct for modelling of age-related macular degeneration disease 2019.

66. Nam U, Lee S, Ahmad A, Yi H-g, Jeon JS. Microphysiological systems as organ-specific in vitro vascular models for disease modeling. BioChip Journal. 2024;18(3):345-56.
67. Li Z, Hu Z, Gao Z. Advances in the Study of Age-Related Macular Degeneration Based on Cell or Cell-Biomaterial Scaffolds. Bioengineering. 2025;12(3):278.

68. Rizzolo LJ, Nasonkin IO, Adelman RA. Retinal cell transplantation, biomaterials, and in vitro models for developing next-generation therapies of age-related macular degeneration. Stem Cells Translational Medicine. 2022;11(3):269-81.

69. DiStefano T, Chen HY, Panebianco C, Kaya KD, Brooks MJ, Gieser L, et al. Accelerated and improved differentiation of retinal organoids from pluripotent stem cells in rotating-wall vessel bioreactors. Stem cell reports. 2018;10(1):300-13.

70. Arik YB. Understanding wet age-related macular degeneration: an organ-on-a-chip model of the outer blood-retinal barrier. 2021.

71. Liu Y-Y, Echeverry-Rendón M. 3D-printed biodegradable polymer scaffolds for tissue engineering: An overview, current stage and future perspectives. Next Materials. 2025;8:100647.

72. Xu F, Dawson C, Lamb M, Mueller E, Stefanek E, Akbari M, et al. Hydrogels for tissue engineering: addressing key design needs toward clinical translation. Frontiers in bioengineering and biotechnology. 2022;10:849831.

73. Nacu I, Bercea M, Niță LE, Peptu CA, Butnaru M, Vereștiuc L. 3D bioprinted scaffolds based on functionalized gelatin for soft tissue engineering. Reactive and Functional Polymers. 2023;190:105636.

74. Wang Q, Wang X, Feng Y. Chitosan hydrogel as tissue engineering scaffolds for vascular regeneration applications. Gels. 2023;9(5):373.

75. Schneider KH, Goldberg BJ, Hasturk O, Mu X, Dötzlhofer M, Eder G, et al. Silk fibroin, gelatin, and human placenta extracellular matrix-based composite hydrogels for 3D bioprinting and soft tissue engineering. Biomaterials research. 2023;27(1):117.

76. Tomić SL, Babić Radić MM, Vuković JS, Filipović VV, Nikodinovic-Runic J, Vukomanović M. Alginate-based hydrogels and scaffolds for biomedical applications. Marine Drugs. 2023;21(3):177.

77. Farzamfar S, Aleahmad M, Gholamreza S, Majid S, Niloofar N. Polycaprolactone/gelatin nanofibrous scaffolds for tissue engineering. Biointerface Res Appl Chem. 2020;11(4):11104-15.

78. Dujardin C, Habeler W, Monville C, Letourneur D, Simon-Yarza T. Advances in the engineering of the outer blood-retina barrier: From in-vitro modelling to cellular therapy. Bioactive Materials. 2024;31:151-77.

79. Rofaani E, Mardani M, Yutiana P, Amanda O, Darmawan N. Differentiation of mesenchymal stem cells into vascular endothelial cells in 3D culture: a mini review. Molecular Biology Reports. 2024;51(1):781.

80. Wei Y, Alexandre U, Ma X. Hydrogels to support transplantation of human embryonic stem cell-derived retinal pigment epithelial cells. Brain Sciences. 2022;12(12):1620.
81. Arpa MD, Akbuğa FJ. Chitosan-based nanogels in modern drug delivery: Focus on protein and gene applications. Gels. 2025;11(9):735.

82. Picado-Tejero D, Mendoza-Cerezo L, Rodríguez-Rego JM, Carrasco-Amador JP, Marcos-Romero AC. Recent advances in 3D bioprinting of porous scaffolds for tissue engineering: a narrative and critical review. Journal of Functional Biomaterials. 2025;16(9):328.

83. Bo T, Pascucci E, Capuani S, Campa-Carranza JN, Franco L, Farina M, et al. 3D bioprinted mesenchymal stem cell laden scaffold enhances subcutaneous vascularization for delivery of cell therapy. Biomedical Microdevices. 2024;26(3):29.

84.Wang J, Cui Z, Maniruzzaman M. Bioprinting: a focus on improving bioink printability and cell performance based on different process parameters. International journal of pharmaceutics. 2023;640:123020.

85. Basyal D, Lee S, Kim HJ. Antioxidants and mechanistic insights for managing dry age-related macular degeneration. Antioxidants. 2024;13(5):568.

86. Pavita PD. Understanding the Mechanisms and Treatment of Age-Related Macular Degeneration (AMD). Scholar's Digest: Journal of Ophthalmology. 2025;1(1):150-66.

87. Isaacson A, Swioklo S, Connon CJ. 3D bioprinting of a corneal stroma equivalent. Experimental eye research. 2018;173:188-93.

88. NIH scientists create eye tissue using 3D bioprinting. Ophthalmology Times [Internet]. 2023 Jan 28 [cited 2026 Jan 29];48(1).

89. Shaw EM, Tate AJ, Periasamy R, Lipinski DM. Characterization of drusen formation in a primary porcine tissue culture model of dry AMD. Molecular Therapy Methods & Clinical Development. 2024;32(4).

90. Bhandari SK, Lee S, Kim HJ. Integrative Landscape of Dry AMD Pathogenesis, Models, and Emerging Therapeutic Strategies. International Journal of Molecular Sciences. 2025;27(1):202.

91. Mimura T, Noma H. Title oxidative stress in age-related macular degeneration: from molecular mechanisms to emerging therapeutic targets. Antioxidants. 2025;14(10):1251.

92. Babapoor-Farrokhran S, Qin Y, Flores-Bellver M, Niu Y, Bhutto IA, Aparicio-Domingo S, et al. Pathologic vs. protective roles of hypoxia-inducible factor 1 in RPE and photoreceptors in wet vs. dry age-related macular degeneration. Proceedings of the National Academy of Sciences. 2023;120(50):e2302845120.

93. Liakopoulos S, von der Emde L, Biller ML, Ach T, Holz FG. Geographic atrophy in age-related macular degeneration. Deutsches Ärzteblatt International. 2025;122(3):82.

94. Song MJ, et al. Bioprinted 3D outer blood-retina barrier model uncovers drivers of age-related macular degeneration. Nat Methods. 2023;20(1):149-162.

95. Liverani C, De Vita A, Minardi S, Kang Y, Mercatali L, Amadori D, et al. A biomimetic 3D model of hypoxia-driven cancer progression. Scientific reports. 2019;9(1):12263.

96. Doktor F, Prager P, Wiedemann P, Kohen L, Bringmann A, Hollborn M. Hypoxic expression of NLRP3 and VEGF in cultured retinal pigment epithelial cells: contribution of P2Y2 receptor signaling. Purinergic Signalling. 2018;14(4):471-84.

97. Ohtonen S. Neurodegeneration linked genetic and environmental factors in in vitro human microglia model: focus on APOE, LRRK2 and traffic-related air pollution. 2024.

98. Falcão AS, Pedro ML, Tenreiro S, Seabra MC. Targeting Lysosomal Dysfunction and Oxidative Stress in Age-Related Macular Degeneration. Antioxidants. 2025;14(5):596.

99. Khalili H, Kashkoli HH, Weyland DE, Pirkalkhoran S, Grabowska WR. Advanced therapy medicinal products for age-related macular degeneration; scaffold fabrication and delivery methods. Pharmaceuticals. 2023;16(4):620.

100. Bharti K, Song MJ, Quinn R, Nguyen E, Park TS, Hampton C, et al. Bioprinted 3D outer retina barrier uncovers RPE-dependent choroidal phenotype in advanced macular degeneration. 2021.

101. Murphy AR, Ng XJ, Lidgerwood G, Pébay A, Truong YB, O'Brien CM, et al. Functionalized collagen I membranes as a Bruch's membrane mimetic for outer retinal in vitro models. ACS Biomaterials Science & Engineering. 2024;10(9):5653-65.

102. Hobbs S, Pierce K. Wet age-related macular degeneration (Wet AMD). 2021.

103. Foss A, Rotsos T, Empeslidis T, Chong V. Development of macular atrophy in patients with wet age-related macular degeneration receiving anti-VEGF treatment. Ophthalmologica. 2022;245(3):204-17.

104. Lim SJ, Gan SC, Ong HT, Ngeow YF. In vitro analysis of VEGF-mediated endothelial permeability and the potential therapeutic role of Anti-VEGF in severe dengue. Biochemistry and Biophysics Reports. 2024;39:101814.

105. Hu D-N, Zhang R, Iacob CE, Yao A, Yang S-F, Chan C-C, et al. Constitutive and hypoxia-induced VEGF production by cultured uveal melanocytes and retinal pigment epithelial cells. Experimental Eye Research. 2025;254:110318.

106. National Institutes of Health (NIH). NIH researchers use 3D bioprinting to create eye tissue: technique provides model for studying genesis of age-related macular degeneration and other eye diseases [Internet]. Bethesda (MD): National Eye Institute (NEI), Ocular and Stem Cell Translational Research Unit; 2022 Dec 22 [cited 2026 Jan 30].

107. Frampton JE. Ranibizumab: a review of its use in the treatment of neovascular age-related macular degeneration. Drugs & aging. 2013;30(5):331-58.

108. Parab M. Developing a 3D Bioprinted model of Pulmonary Veins to investigate altered endothelial cell signaling in Hypoxia. 2025.

109. Dujardin C. Development of a 3D pre-vascularized structured hydrogel membrane for outer blood-retinal barrier modelling and therapy for choroidal dystrophies: Université Paris Cité; 2024.

110. Ruiz EAC, Swindle-Reilly KE, Versypt ANF. Experimental and mathematical approaches for drug delivery for the treatment of wet age-related macular degeneration. Journal of Controlled Release. 2023;363:464-83.

111. Anthon SG, Valente KP. Vascularization strategies in 3D cell culture models: from scaffold-free models to 3D bioprinting. International journal of molecular sciences. 2022;23(23):14582.

112. Wang M, Li H, Wang F. Roles of transepithelial electrical resistance in mechanisms of retinal pigment epithelial barrier and retinal disorders. Discovery Medicine. 2022;34(171):19-24.

113. Cenhrang K. 3D Printed Devices With Integrated Scaffolds for Microfluidic-Based Transwell Cell Culture Studies: Saint Louis University; 2025.

114. Supjaroen P, Niamsi W, Thummarati P, Laiwattanapaisal W. An In Vitro Cell Model of Intestinal Barrier Function Using a Low-Cost 3D-Printed Transwell Device and Paper-Based Cell Membrane. International Journal of Molecular Sciences. 2025;26(6):2524.

115. Kim J, Park JY, Kong JS, Lee H, Won JY, Cho DW. Development of 3D printed Bruch's membrane-mimetic substance for the maturation of retinal pigment epithelial cells. International Journal of Molecular Sciences. 2021;22(3):1095.

116. Swinkels M, Atiq F, Bürgisser PE, Slotman JA, Houtsmuller AB, de Heus C, et al. Quantitative 3D microscopy highlights altered von Willebrand factor α-granule storage in patients with von Willebrand disease with distinct pathogenic mechanisms. Research and Practice in Thrombosis and Haemostasis. 2021;5(6):e12595.

117. Boutin M, Hampton C, Quinn R, Ferrer M, Song M. 3D engineering of ocular tissues for disease modeling and drug testing. Pluripotent Stem Cells in Eye Disease Therapy: Springer; 2019. p. 171-93.

118. Evers III CD, Chen L, Messinger JD, Killingsworth M, Freund KB, Curcio CA. Histology, dimensions, and fluorescein staining characteristics of nodular and cuticular drusen in age-related macular degeneration. Retina. 2023;43(10):1708-16.

119. Kar SS, Cetin H, Abraham J, Srivastava SK, Madabhushi A, Ehlers JP. Combination of optical coherence tomography-derived shape and texture features are associated with development of sub-foveal geographic atrophy in dry AMD. Scientific Reports. 2024;14(1):17602.

https://doi.org/10.22034/jrb.2026.07.V2I1A8

120. Shetty SD. Fundus Fluorescein Angiography as a Diagnostic Tool in Age Related Macular Degeneration: Rajiv Gandhi University of Health Sciences (India); 2018.

121. Huo T, Zhou L, Bian X, Wen Y. Advancing microneedle technology for multiple distinct target organs drug delivery through 3D printing: a comprehensive review. Advanced Composites and Hybrid Materials. 2025;8(3):266.

122. Ciszewski P, Drelichowska A, Pikor D, Wiśniewska E, Azierski M. Innovative technologies for the treatment of dry age-related macular degeneration (AMD)-modern therapeutic perspectives and their future. Romanian Journal of Ophthalmology. 2025;69(1):10.

123. Lu R. Advances in Ophthalmic Organ-on-a-Chip Models: Bridging Translational Gaps in Disease Modeling and Drug Screening. International Journal of Translational Medicine. 2024;4(4):710-25.

124. Liu H, Lin DWS, Parikh BH, Hao M, Tan QSW, Chee PL, et al. Single-cell-pore-sized 3D printed scaffolds for retinal pigment epithelial cell therapy. Acta Biomaterialia. 2025.

125. Chung M, Lee S, Lee BJ, Son K, Jeon NL, Kim JH. Wet-AMD on a chip: Modeling outer blood-retinal barrier in vitro. Advanced healthcare materials. 2018;7(2):1700028.

126. Singh M, Negi R, Alka, Vinayagam R, Kang SG, Shukla P. Age-related macular degeneration (AMD): pathophysiology, drug targeting approaches, and recent developments in nanotherapeutics. Medicina. 2024;60(10):1647.

127. Qu S, Lin H, Pfeiffer N, Grus FH. Age-related macular degeneration and mitochondria-associated autoantibodies: a review of the specific pathogenesis and therapeutic strategies. International Journal of Molecular Sciences. 2024;25(3):1624.

128. Galindo-Camacho RM, Blanco-Llamero C, da Ana R, Fuertes MA, Señoráns FJ, Silva AM, et al. Therapeutic approaches for age-related macular degeneration. International journal of molecular sciences. 2022;23(19):11769.

129. Auel T, Großmann L, Schulig L, Weitschies W, Seidlitz A. The EyeFlowCell: development of a 3D-printed dissolution test setup for intravitreal dosage forms. Pharmaceutics. 2021;13(9):1394.

130. Wu KY, Osman RM, Esomchukwu O, Marchand M, Nguyen BH, Tran SD. Advances in Regenerative Medicine, Cell Therapy, and 3D Bioprinting for Glaucoma and Retinal Diseases. Cell Biology and Translational Medicine, Volume 25: Advances in Regenerative Medicine and Cellular Therapy. 2025:115-39.

131. Tang Z, Ye F, Ni N, Fan X, Lu L, Gu P. Frontier applications of retinal nanomedicine: progress, challenges and perspectives. Journal of nanobiotechnology. 2025;23(1):143.

132. Hamdy NM, Basalious EB, El-Sisi MG, Nasr M, Kabel AM, Nossier ES, et al. Advancements in current one-size-fits-all therapies compared to future treatment innovations for better improved chemotherapeutic outcomes: a step-toward personalized medicine. Current medical research and opinion. 2024;40(11):1943-61.

133. Tisi A, Feligioni M, Passacantando M, Ciancaglini M, Maccarone R. The impact of oxidative stress on blood-retinal barrier physiology in age-related macular degeneration. Cells. 2021;10(1):64.

134. Benboubker V, Ramzy GM, Jacobs S, Nowak-Sliwinska P. Challenges in validation of combination treatment strategies for CRC using patient-derived organoids. Journal of Experimental & Clinical Cancer Research. 2024;43(1):259.

135. Tan S, Qiu L, Lee JWL, Zeng L. Advances in 3D bioprinting for modeling the blood-brain barrier in neurodegenerative diseases. Frontiers in Molecular Biosciences. 2025;12:1703403.

136. Finny AS. 3D bioprinting in bioremediation: a comprehensive review of principles, applications, and future directions. PeerJ. 2024;12:e16897.

137. Wang MH. Integrating Artificial Intelligence and Precision Therapeutics for Advancing the Diagnosis and Treatment of Age-Related Macular Degeneration. Bioengineering. 2025;12(5):548.

138. Gangadevi E, Shri ML, Dhanaraj RK, Balusamy B. Computational Intelligence in Bioprinting: Challenges and Future Directions: John Wiley & Sons; 2024.

139. Rasekh M, Arshad MS, Ahmad Z. Advances in Drug Delivery Integrated with Regenerative Medicine: Innovations, Challenges, and Future Frontiers. Pharmaceutics. 2025;17(4):456.

140. Teli P, Kale V, Vaidya A. Beyond animal models: revolutionizing neurodegenerative disease modeling using 3D in vitro organoids, microfluidic chips, and bioprinting. Cell and Tissue Research. 2023;394(1):75-91.

141. Liu S, Jin P. Advances and Challenges in 3D Bioprinted Cancer Models: Opportunities for Personalized Medicine and Tissue Engineering. Polymers. 2025;17(7):948.