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Review

Advancing Precision Ophthalmology: Human Retinal Organoids as Platforms for Disease Modeling and Personalized Therapy

Evan Paul Zelt [1,2,*], Sachdeep Singh [1,3], Magdalene J. Seiler [4], Hu Huang [3,5], Anthony Atala [1], Jian-Xing Ma [3,5] and Yuanyuan Zhang [1,3]

[1] Wake Forest Institute for Regenerative Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA
[2] Wake Forest School of Medicine, Winston-Salem, NC 27101, USA
[3] Translational Eye and Vision Research (TrEVR) Center, Wake Forest School of Medicine, Wake Forest University, Winston-Salem, NC 27101, USA
[4] Departments of Physical Medicine and Rehabilitation, Ophthalmology and Visual Science, Anatomy and Neurobiology, University of California, Irvine (UCI), Irvine, CA 92697, USA
[5] Department of Biochemistry, School of Medicine, Wake Forest University, Winston-Salem, NC 27101, USA
* Correspondence: evan.zelt@wfusm.edu

Abstract

Human-induced pluripotent stem cell (hiPSC)-derived retinal organoids (ROs) have emerged as a transformative 3D in vitro model that closely recapitulates human retinogenesis and the layered cellular architecture of the native retina. This review highlights their profound utility as a precision platform for ophthalmic research. ROs, particularly those derived from patients with inherited retinal diseases (IRDs), provide an effective model for investigating disease pathogenesis, while retaining the patient's genetic background. This specificity is crucial for the modeling of monogenic disorders like Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA) and complex conditions like Age-Related Macular Degeneration (AMD), Diabetic Retinopathy (DR), and battle-related ocular trauma in the battlefield. Furthermore, ROs serve as a scalable and high-throughput tool for drug screening and toxicology testing, accelerating the identification of therapeutic compounds. Finally, they represent a renewable source for generating purified, functional retinal cells (e.g., photoreceptors and retinal ganglion cells) for precision cell therapies aimed at retinal repair. While challenges remain in achieving true vascularization and long-term maturation, RO technology is poised to rapidly advance personalized medicine and curative strategies for blinding retinal disorders.

Keywords: retinal organoids; induced pluripotent stem cells; precision medicine; disease modeling; inherited retinal diseases; ocular trauma in the battlefield; photoreceptors; age-related macular degeneration; diabetic retinopathy; drug screening; cell therapy

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1. Introduction

Retinal diseases, including Inherited Retinal Diseases (IRDs), Age-Related Macular Degeneration (AMD), and Diabetic Retinopathy (DR), are leading causes of irreversible vision loss globally [1]. Traditional research models, primarily two-dimensional cell cultures and animal models, often fail to accurately replicate the complex human retinal environment, layered structure, and unique pathobiology of these human-specific genetic diseases. Retinal organoids (ROs) overcome these limitations by allowing human stem cell-derived retinal cells to self-organize into a stratified, three-dimensional structure. This provides a system that is highly relevant to human pathophysiology.

Current RO protocols can generate the seven major retinal cell types: photoreceptors (rods and cones), bipolar cells, amacrine cells, horizontal cells, Müller glia, and retinal ganglion cells (RGCs) [2,3]. In addition to generating the major retinal cell types, ROs have demonstrated functional properties such as light sensitivity [4–7]. Patient-derived ROs have been established for numerous IRD-causing gene mutations [8,9]. They are increasingly used to investigate disease-specific phenotypes, therapeutic responses, and pathogenic mechanisms across the spectrum of more than 300 IRD-associated genes [10]. Advanced co-culture and bioengineering techniques are enabling the development of more complex models that incorporate additional essential cell types [5,11].

The main challenges associated with ROs include incomplete maturation, lack of vascularization, and limited reproducibility. Achieving the full morphological and functional maturity of native adult photoreceptors and RGCs remains difficult, limiting the ability of ROs to model late-onset diseases. Additionally, current ROs lack a functional blood–retina barrier and an intrinsic vasculature, limiting their use in modeling diseases such as Neovascular AMD and advanced DR. Furthermore, current RO protocols have reproducibility issues that reduce efficiency and increase variability across induced pluripotent stem cell (iPSC) lines and production batches, particularly in large-scale drug screening applications [12,13].

The core rationale for utilizing ROs derived from human embryonic stem cells (hESCs) and hiPSC is to provide a patient-specific, three-dimensional, and developmentally accurate model. ROs derived from patient-derived cells (Table 1) inherently retain the donor's unique genetic background, allowing researchers to observe disease mechanisms specific to individual mutations and genetic modifiers [9]. The 3D architecture of the RO facilitates cell-to-cell communication and stratification, which is vital for studying complex mechanisms of disease that rely on layered retinal organization, such as those involving the photoreceptor–RPE interface (AMD, Stargardt disease) or inner retinal circuits (glaucoma, DR). The human context offers a more reliable predictor of a drug's efficacy and potential toxicity in human iPSC-derived ROs compared to animal or 2D models.

Table 1. Common Origins for iPSCs.

Cell Type	Features
Peripheral Blood Mono Nuclear Cells [14,15]	Blood sampling is well established Requires more timely handling
Urine-derived Stem Cells (USCs) [16–18]	Accessible sampling May produce lower yields
Dermal Fibroblasts [14,19,20]	Easily accessible but retrieval may result in scarring Less genetic homogeneity (variance with site of biopsy)

Retinal organoid technology is dramatically reducing reliance on less predictive animal models and accelerating the pace of translational research. It provides a unique time window into the earliest stages of human retinogenesis and disease onset, which are often inaccessible in vivo. The long-term goal is to develop a fully bio-engineered integral retinal unit (Table 2) that includes the neural retina, RPE, and a functional vascular supply to serve as an ultimate preclinical testing platform and a scalable source of transplantable cells for personalized regenerative medicine.

Table 2. In Vitro 3D Retinal Structural Approaches.

Structure	Description
Retinal Spheroids [21,22]	3D Organization in spherical shape Singular or few undifferentiated cell type/types No complex organization of tissue types Usually simpler to produce
Retinal Organoids [2,23,24]	Functionally and structurally resembles the native retina Stratification of retinal cell layers Indicated for many uses such as disease modeling, gene therapy, and regenerative medicine
Retinal Organoid on a Chip [25,26]	Dynamic culture media delivery apparatus Provides a protective environment for organoids Media monitoring with higher consistency Higher quality RPE-photoreceptor interactions
Tissue Engineering [27,28]	Engineered with scaffolds of various materials Greater uniformity, complexity, and integration for transplant purposes Can use materials to create scaffold-free structures after growth

The proposed innovations for leveraging ROs are focused on enhancing model complexity and clinical application. These include the development of vascularized and microglia-integrated ROs through advanced co-cultures to model the inflammatory and vascular components of complex diseases like AMD, DR, and glaucoma [29,30]. To measure RO health non-invasively, implementing advanced electrophysiological and optical tools (e.g., multielectrode arrays, calcium imaging) provides quantitative, functional measurements, rather than relying solely on morphology [25,31].

ROs may be leveraged using CRISPR/Cas9 to correct a patient's genetic mutation in the hiPSCs to generate isogenic control organoids. These allow for definitive attribution of the observed developmental pathology to the specific gene variants, thus increasing the model's robustness for personalized drug screening.

Patient-derived ROs with genetic mutations for IRDs (e.g., RPGR) can accurately reproduce key disease phenotypes, such as cilial defects and accelerated photoreceptor loss, that are not present in isogenic gene-corrected control ROs [32,33]. By using RO-based high-throughput screens, therapeutic compounds may achieve a higher success rate in preventing retinopathies compared to compounds identified using traditional 2D models. Additionally, photoreceptors and RGCs purified from mature, gene-corrected hiPSC-derived ROs may have the capacity to perform superior integration and long-term functional survival after transplantation into recipient retina models compared to cells derived from traditional 2D culture methods.

The impact of the advancing RO technologies is profound and multi-layered. For one, ROs fundamentally transform the study of human retinogenesis and disease pathobiology, moving from correlational animal data to direct, human-relevant data. Also, ROs accelerate the transition to personalized medicine by enabling testing of therapeutic interventions on an individual patient's retinal cells in vitro. For example, ROs may be used to validate

vectors and screen for toxicity in AAV-mediated gene therapies [34]. By increasing the success rate of preclinical drug development and providing a scalable, non-controversial source of cells for transplantation, the RO platform may be able to reduce societal and healthcare burdens associated with irreversible blindness.

2. Retinal Organoid Differentiation Protocols

To provide structural and functional platforms suitable for high-throughput drug screening and precision medicine, the field relies on two distinct types of differentiation protocols (Figure 1).

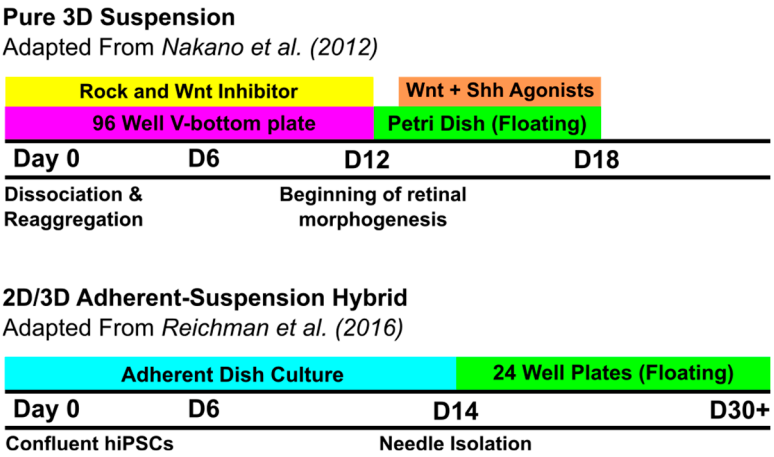


Figure 1. Overview of Timeline for Retinal Organoid Differentiation Method Types.

2.1. Pure 3D Suspension Protocols

These methods rely on the intrinsic self-organizing capacity of hiPSCs. Single-cell suspensions are re-aggregated in low-attachment V-bottom or U-bottom wells to form uniform embryoid bodies (EBs). Remarkably, these cultures showed self-organization and retinal differentiation with little exogenous growth factors, such as Wnt and BMP inhibitors, when first shown in mouse ESCs [23]. In human ESCs, culture medium was optimized for neural retina formation with the addition of various exogenous modulators, such as Wnt inhibitors and BMP antagonists [24]. Recent studies investigated the addition of other growth factors in these suspension cultures [35,36].

2.2. 2D/3D Adherent-Suspension Hybrid Protocols

To circumvent the efficiency limitations of pure suspension protocols, transitional protocols introduced an adherent phase to facilitate the manual selection of eye field structures. Notably, this method did not require the use of signaling factors like Wnt/BMP antagonists to achieve efficient differentiation of neural retina and RPE cell types [37–39]. Other protocols began with the formation of EBs that were then seeded to form an adherent culture for the generation of eye domains [4,40]. Each of these methods mechanically removed eye field structures from the 2D culture. These structures were transferred to suspension culture for long-term maturation. As they matured, they experienced stratification of retinal layers [4].

3. Ideal Retinal Organoids

The search for an 'ideal' RO has resulted in the procurement of a variety of methods to enhance the physiological likeness of these models using the addition of various tissues and biomechanical devices. There appears to be 5 major goals for the use of ROs. These

can be classified as isogenic control, drug testing, cell therapy, disease modeling, and structural definition.

With gene editing technologies, ROs can undergo disease-relevant phenotypic shifts [41]. This has many implications for the use of ROs in disease and pharmaceutical research. These include gene identification of pathogenic variants [42] and testing for corrective therapies [32].

ROs have the potential to be used in drug testing environments. They display similar physiologic responses to known retinotoxins as are seen in the native human retina [43], supporting their use to screen novel drugs for toxicity. Further, ROs have already been used to measure drug efficacy and toxicity profiles using cellular responses to candidate anti-tumor drugs [44]. In combination with emerging microfluidic technology [25], ROs may provide a high-throughput platform to reliably improve drug development and screening.

Novel cellular therapies [45–48] are a notable indication for the procurement of mature and selective ROs. There are a variety of approaches to these therapies including sheet integration [45,46], injection of purified cellular suspensions [47], and bio-engineered scaffold implantation [48]. These ROs are optimized for their function by improving maturity and structural organization to maximize their integrative and therapeutic potential.

Disease modeling can be performed using the RO platform. In general, diseases modeled with ROs can be grouped into inherited diseases [41,42], multifactorial diseases [49,50], and trauma [51]. The generation of these ROs is highly variable across diseases of interest.

Structural definition of tissue is important to many studies, and ROs can provide great versatility in methods of histological analysis. They can be supported by additional tissues, as seen in cases of co-culturing methods, to enhance maturation [11]. Additionally, gene-edited progenitors allow for the inclusion of knock-in reporter sequences to follow sequences such as self-organization [52,53]. These may be helpful in standardizing RO generation protocols and following disease progression.

4. Cell Replacement Therapies

One potential use for human-derived ROs is the procurement of human retinal cells. Many retinal diseases result in the loss of cells in the layers of the retina and cause progressive loss of vision. Future therapeutic treatments for vision loss may include the administration of cells cultured in vitro that are descended from a patient or a human donor. With the versatility and control of RO development in a lab environment, procedures may be adjusted to increase the yield of desired cell types [54,55]. These therapies leverage the organoid's ability to produce mature and stratified retinal tissue or highly purified progenitor cells for transplantation.

4.1. Photoreceptor Precursor Cells

These cells are sourced from fully laminated retinal organoids, which are differentiated long-term in 3D suspension cultures. These organoids self-organize into an optic cup-like structure, consisting of the major retinal layers. Importantly, the Outer Nuclear Layer (ONL) is formed, containing both rod and cone photoreceptors. From the organoids, a single cell suspension is produced, in which various procedures for the selective enrichment of photoreceptor precursor cells (PRPCs) may take place [56,57]. These cells can be purposed to replace damaged or lost photoreceptors in diseases such as Retinitis Pigmentosa, where inner retinal neurons (bipolar, amacrine, and retinal ganglion cells) may survive. This could be achieved through an injection of the transplanted PRPCs into the subretinal space, where they may be able to integrate into the host retina. To isolate the PRPCs from the organoids, various techniques have been attempted and refined for clinical-grade manufacturing, including cell sorting with flow cytometry and selective disassociation

with enzymes. Isolation of photoreceptor precursor cells using flow cytometry combines negative selection of the CD29 and SSEA-19 biomarkers and positive selection of CD73 (CD29-/SSEA-19-/CD73+) [56,57]. Enzymatic isolation of photoreceptors leverages the organization of layers of the RO by removing photoreceptor cell-containing supernatant at earlier timepoints after the introduction of dissociative enzymes [58].

4.2. Retinal Pigment Epithelium (RPE) Monolayers/Sheets

While RPE cells can be differentiated in 2D culture, they are also derived from the same early retinal lineage as neural retinal cells in the 3D-shaped ROs. In some RO differentiation protocols, it is possible to derive RPE cells in patches adjacent to the neural retina. These cells may be isolated and expanded in 2D culture to produce an RPE monolayer, which has potential to replace degenerated RPE [59]. Certain disease stages are notable for RPE degeneration, such as the geographic atrophy stage of age-related macular degeneration (AMD) [60]. Transplantation of an RPE monolayer into the subretinal space has been proposed as a method to replace the degenerated native tissue [61]. There are several clinical trials investigating the safety of this surgical procedure in patients [62]. Integration of the layer has the potential to restore the outer blood–retina barrier and provide phagocytic and metabolic support to overlying photoreceptors, preventing future cell stress.

4.3. Retinal Progenitor Cells (RPCs)

RPCs belong to immature cell types that are dominant in early ROs. Progenitors are a source of multipotent cells that can be banked with cryopreservation for later use [63]. These cells are both highly proliferative and versatile, making them useful for long-term storage while maintaining multipotency and the ability to expand. RPCs derived from hiPSCs have shown integrative capacity when transplanted in mice [64], suggesting that they may provide a source of functional cells for tissue regeneration. A potential drawback to the increased pluripotency of these cells is the associated risk of uncontrolled proliferation and teratoma formation.

4.4. Utilizing Retinal Organoids in Clinical Settings

The utilization of ROs for patient therapies involves a multitude of translational and logistical challenges. For one, delivering individualized organoid-derived treatment requires validation of cGMP, which can become highly cost-prohibitive. Beyond costs, variability plays a central role in achieving good outcomes. Particularly, photoreceptor rosette formation has been shown to be problematic in the process of subretinal transplantation of RO-derived sheets [65]. Rossette formation and other reproducibility issues are being addressed through the utilization of bioreactors to standardize RO generation [66].

5. Retinal Organoids for Drug Development and Testing

There is evidence that retinal organoids accurately model drug effects that occur in vivo, providing indication for their use in toxicological screening [43]. 3D ROs for drug testing are categorized by their accuracy in recapitulating a particular disease process or reproducing a specific physiological function. Additionally, these ROs can be formed from patient-derived hiPSCs. Patient-specific drug testing can be performed by measuring physiologic responses to available or novel drugs before administration to the patient. This facet of personalized medicine could have major implications for the advancement of patient safety and outcome improvement in the settings of experimental drugs or drugs with narrow therapeutic windows. These advantages may be limited by the time required to observe changes in mature ROs.

5.1. Standard Laminated Retinal Organoids

These are standard organoids that contain the key cell types of the neural retina in laminated layers. These types include photoreceptors, retinal ganglion cells, bipolar cells, horizontal cells, amacrine cells, and Müller glia. The applications of these organoids are widespread and include retinotoxicity screening, IRD modeling, and drug efficacy testing. Introducing toxic compounds to ROs can reveal cellular stress responses, as shown in a study evaluating retinal exposure to bisphenols [67]. IRDs may be studied with the model organoids (Figure 2) derived from hiPSCs of the patients with those diseases, including Retinitis Pigmentosa and Leber Congenital Amaurosis [32,68]. Efficacy testing can be used to determine a proposed therapeutic's ability to promote and protect visual cycle function. The limitations of standard laminated retinal organoids include the lack of a native blood supply, heterogeneity of cells, and the extensive time required for cultures [69].

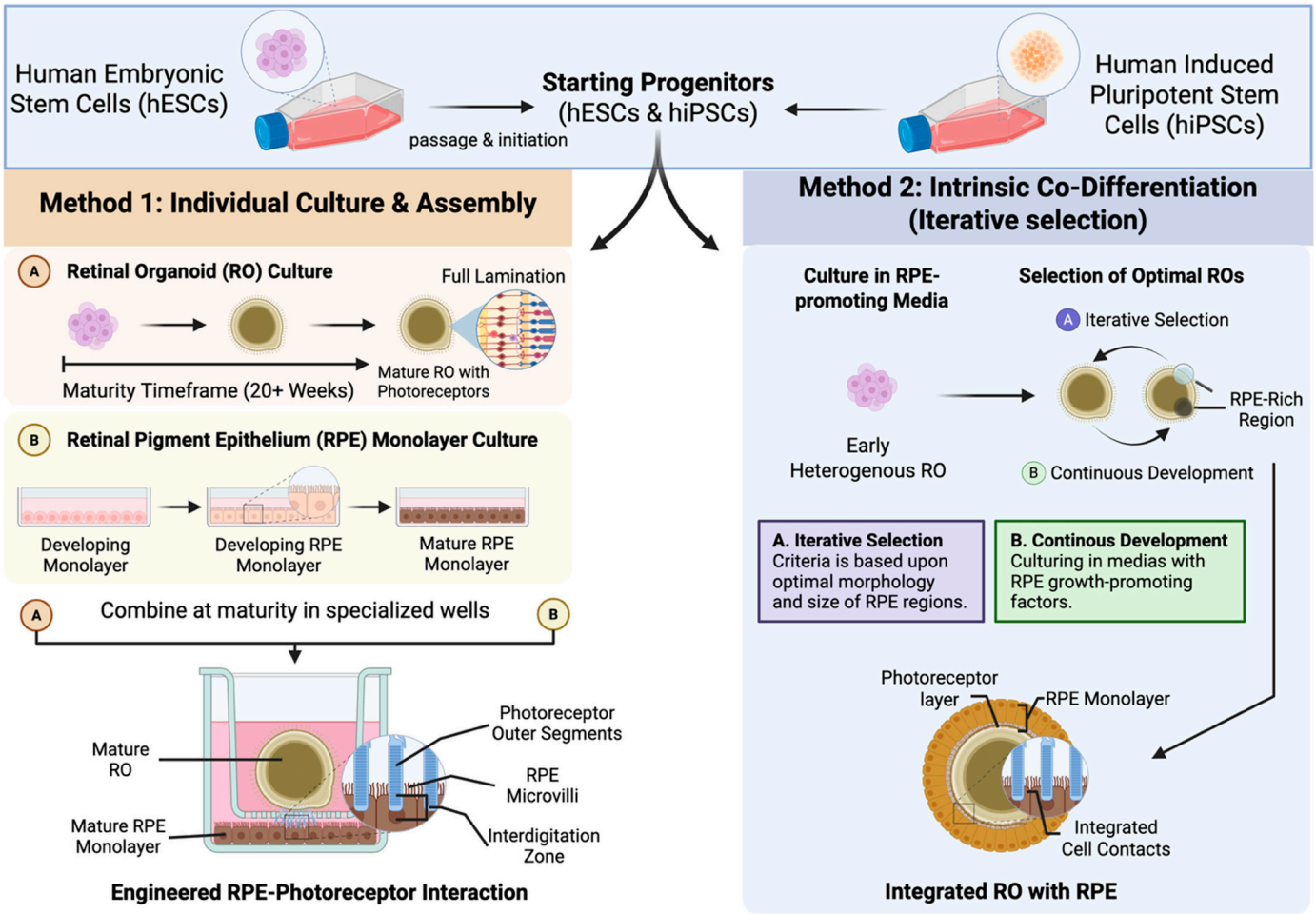


Figure 2. Methods for Producing Retinal Organoids with RPE. Method 1 involves individually culturing pluripotent stem cells (ESCs and iPSCs) to generate separate retinal organoids and RPE monolayers. Once mature, these cultures are combined in specialized wells designed to facilitate interaction between the RPE and photoreceptors. In contrast, Method 2 utilizes pluripotent stem cells to iteratively select retinal organoids with larger, RPE-rich regions. This approach relies on specialized culture media supplemented with factors that promote both RPE growth and its characteristic interaction with photoreceptors.

5.2. Co-Culture Models

These are models consisting of the neural retina and RPE layer that are designed to capture the functional relationship between the two layers. These cultures are formed

through the direct co-culture of an RPE monolayer with the RO [11], or with the use ofTf protocols that favor the spontaneous generation of RPE patches [59] (Figure 2, Table 3). As a crucial part of the visual cycle, this layer recycles important signal transduction molecules and phagocytoses the outer segments of photoreceptors. AMD is a disease marked by the degeneration of photoreceptors, whose modeling accuracy may be improved with accelerated differentiation in co-culture [70]. Additionally, these co-culture models may recapitulate a more physiologically accurate microenvironment for drug development [71].

Table 3. Comparison of Methods to Produce Retinal Organoids with RPE.

Method	Advantages	Disadvantages
Parallel Differentiation & Co-Culture [11]	Control over interface between RPE and photoreceptors Ability to utilize control and experimental/ treatment groups	Complicated culture logistics Specialized interfacing wells required Greater variability in the combination of cultures
Spontaneous Enhancement [59]	Native interface between RPE and photoreceptors	Lower culture yield Interaction dependent on variable morphology

5.3. Vascularized Retinal Organoids (VROs)

These cultures seek to address the limitation that standard retinal organoids lack a native blood supply. They do so by introducing vascular endothelial cells and pericytes to initiate the formation of blood vessel-like structures in the retinal organoid or by co-culturing ROs with blood vessel/vascular organoids [5,6]. These organoids provide pathways for studying the breakdown of the blood–retina barrier and neovascularization (as seen in proliferative diabetic retinopathy). VROs may be used to identify mechanisms and discover drugs to advance the treatment of retinal vascular disorders [30]. Similarly to RPE co-cultures, these organoids are limited by the increased complexity of their cultures. Additionally, they present challenges in controlling perfusion of natural blood flow. Lack of perfusion limits the modeling of thrombotic events as seen in vein and artery occlusions of the retina [30]. Some techniques for the creation of VROs include co-aggregation [30] and discrete fusion [5]. These techniques differ based on the maturity of the RO at the time of combination. In coaggregation, RO differentiation begun with the inclusion of vascular cells, while discrete fusion added vascular organoids to mature ROs.

5.4. Retinal Organoids Integrating Microglial Cells

Cultures involving microglial cells are valuable to the study of drug development as they can display characteristics of immune competency [29]. As many pathologies may include immune systems, it is vital that these processes are present in RO models [72]. Additionally, immune responses can be relevant to drug screening processes [73] and may affect candidate therapies due to limited acceptable doses.

5.5. Retinal Organoids in Micro-Physiological Systems (MPSs)

Devices such as organ on a chip or microfluidic devices can be paired with retinal organoids to provide control over nutrient delivery, waste removal, and mechanical force [28]. These models provide higher throughput than traditional methods due to their compactness and automated perfusion of tissue [25,26]. They can be used to screen large quantities of compounds. Additionally, they may be integrated with multiple-organ-chip devices to perform systemic toxicity screening [74].

6. Types of 3D Retinal Organoids for Disease Modeling

6.1. Inherited Retinal Disease (IRD) Models

This is a common application for retinal organoids, as patient-derived iPSCs provide the precise genetic makeup to recapitulate the disease process for observation of the underlying mechanisms (Table 4).

Table 4. Genetic Profiles and Cellular Features of Key Inherited Retinopathies.

Modeled Disease	Cellular/Genetic Features
Retinitis Pigmentosa [75–78]	Various gene mutations (e.g.,) that lead to the degeneration of rod and cone photoreceptor and defects in cilial and outer segment structure.
Leber Congenital Amaurosis [79,80]	Models of defective genes such as RPE and AIPL1. Focused on early photoreceptor development abnormalities. Other recapitulated features include phototransduction and visual cycle defects.
Stargardt Disease [81]	ABCA4 mutations that lead to photoreceptor defects and accumulation of toxic lipofuscin-like material.
Usher Syndrome [82,83]	Various mutations (e.g., USH2A, PCDH15) that alter the structure of connecting cilium in photoreceptors (also seen in sensorineural cells).
X-linked Juvenile Retinoschisis [84]	RS1 mutations that lead to loss of cell-to-cell adhesion results in degraded layer integrity and synaptic defects.

6.2. Multifactorial Disease Models

These models induce pathological conditions in the organoid or incorporate additional cell types to accurately reflect the complexity of the disease in vivo (Table 5) [85–87].

Table 5. Pathological Features and Induction Methods of Multifactorial Disease Models.

Modeled Disease	Cellular/Pathological Features
Age-Related Macular Degeneration [50,85,88]	Exposure of oxidative stress or use of iPSC-derived genetic risk factors. Focused on the degeneration of RPE cells and photoreceptors.
Diabetic Retinopathy [49,86,89]	Induced through exposure of hyperglycemic conditions that mimic the diabetic environment. Focused on neurodegeneration and low-grade inflammation.
Glaucoma [87]	Increased loss of retinal ganglion cells. Limited by the lack of a full optic nerve structure.
Retinoblastoma [90,91]	RB1-mutant ROs focused on the study of initiation and progression of this retinal tumor.

Abbreviations: iPSC: Induced Pluripotent Stem Cell; RPE: Retinal Pigment Epithelium, RO: Retinal Organoid.

6.3. Composite Organoid Models

These are more complex co-culture models that aim to overcome the limitations of the basic retinal organoid, including the lack of a vascular supply, a robust RPE-PR interaction, and immune surveillance (Table 6).

Table 6. Features and Applications of Composite Organoid Models.

Organoid Type	Feature	Disease Modeled
Vascularized Retinal Organoids [5,30,92]	Endothelial cells to form basic blood vessel structures to mimic the retina's vascular network.	Wet / Neovascular AMD
Retinal-RPE-Choroid/Tri layer Organoids [93,94]	Multi-culture of the retinal organoid (neural retina) with both RPE and choroid-like cultures.	Diseases involving the entire outer retinal complex, including advanced AMD
Microglia-integrated Retinal Organoids [5]	Addition of microglial cells to the retinal organoid	Immune response-involved diseases such as glaucoma and diabetic retinopathy

Abbreviations: AMD: Age-Related Macular Degeneration; RPE: Retinal Pigment Epithelium.

7. 3D Retinal Organoids for Battlefield Ocular Trauma Modeling

The transition from anterior segment trauma to permanent retinal vision loss is a complex pathological cascade often initiated by battlefield injuries. There are a variety of injuries associated with the battlefield environment (Table 7) [95]. While corneal lacerations and blast-induced ocular surface damage represent the immediate clinical presentation in the field, these injuries frequently trigger a generalized ocular inflammatory response.

Table 7. Common Ocular Injuries in the Battlefield Environment.

Injury Type	Mechanism of Trauma	Resulting Pathophysiology	Modeling Approach
Corneal Laceration [95]	Shrapnel, projectiles, or debris.	Open globe, loss of IOP, risk of endophthalmitis.	Porcine/Rabbit ex vivo models;
Blast Overpressure [95]	Explosive shockwaves (IEDs).	Retinal apoptosis, optic nerve stretching, RPE shearing.	Shock tube blast models (Rat/Mouse); Ultrasound-induced stress.
Retinal Fibrosis/PVR	Secondary to penetrating trauma or chronic inflammation.	Tractional retinal detachment; epithelial–mesenchymal transition (EMT).	iPSC-derived RPE wound healing assays; Tri layer organoids.
Chemical/ Thermal Burns [95]	Incendiary devices or caustic agents.	Limbal stem cell deficiency; corneal opacification.	Corneal epithelial co-culture; Amniotic membrane scaffolds.

Abbreviations: IOP: Intraocular Pressure; IED: Improvised Explosive Device; PVR: Proliferative Vitreoretinopathy; RPE: Retinal Pigment Epithelium.

7.1. Corneal Trauma Modeling

Corneal injury models, such as those utilizing photoactivated Rose Bengal for laceration sealing, highlight the importance of immediate stabilization [96]. However, without rapid intervention, anterior segment trauma initiates a cascade of inflammatory cytokines and growth factors that migrate to the posterior segment. Using Microglia-integrated Retinal Organoids (Table 6), researchers could model how these systemic and anterior-derived inflammatory signals trigger retinal microglia activation. The "Injury-on-a-dish" approach may allow for the study of treatments for Retinal Fibrosis and Proliferative Vitreoretinopathy (PVR), conditions that Dr. Wang's research has identified as major complications following combat ocular trauma [97,98]. Such an approach could involve similar methods performed in animals, such as scratch assays, to accurately model traumatic conditions. Modeling trauma with human ROs could provide many advantages, especially in the development of anti-inflammatory and anti-fibrotic therapies due to the availability of high-throughput systems for ROs. While these models may be useful for the retina's responses to injury, there are currently no organoids that accurately include a cornea–aqueous–vitreous–retina connection to model the origination and propagation of the inflammatory cascade related to corneal laceration.

7.2. Ultrasound and Blast-Induced Retinal Injury

In addition to mechanical trauma, the battlefield environment exposes service members to blast overpressure and high-intensity waves. Experimental models have utilized ultrasound-induced injury and blast shock tubes to simulate these non-penetrating traumas. These models demonstrate that repetitive low-level blast exposure leads to significant apoptosis in the neuroretina and optic nerve [51]. Retinal organoids provide a unique platform to subject neural tissue to controlled ultrasonic or mechanical stress, allowing for the quantification of RGC loss and the testing of neuroprotective small molecules, such as RUNX1 inhibitors, to mitigate post-traumatic damage [99].

8. Overcoming Current Limitations in Organoid Fidelity

Despite their potential, the current generation of retinal organoids faces structural and functional hurdles that impact their model fidelity to resemble the adult human retina [100]. A primary limitation is the inability to achieve complete structural maturation. Due to the lack of endogenous vascularization and variable spatial integration with the retinal pigment epithelium (RPE), photoreceptors often fail to reach the outer segment maturity seen in vivo. This constraint has historically limited the modeling of late-onset degenerative diseases and the long-term evaluation of cell therapies [101].

Recent bioengineering advancements are beginning to address these gaps. The integration of endothelial cells has shown significant promise in extending organoid maturity. For instance, ROs have been successfully vascularized through co-culture with vascular organoids, mimicking the retina's complex nutrient delivery system [4–6]. Furthermore, because microglia are not derived from retinal neuroectoderm, traditional ROs lack the machinery to model neuroinflammation [102]. However, the addition of iPSC-derived microglia to RO cultures now provides a robust platform for studying immune-involved pathologies such as Age-Related Macular Degeneration (AMD) and Diabetic Retinopathy (DR) [29].

The lack of an optic nerve head, which is a major barrier in glaucoma research using ROs, is being addressed through multisystem engineering. Recent studies have reported the projection of optic nerve-like fiber bundles when ROs are cultured in proximity to brain organoids, paving the way for a novel co-culture [103]. Overall, the integration of non-neural retinal cells into culture with ROs presents opportunities to study additional ocular

disease mechanisms. They introduce the ability to study the interaction of tissues with the neural retina and establish targets to prevent retinal degeneration in these diseases [103].

Finally, a major limitation of ROs is the lack of major ocular structures including the cornea, lens, lacrimal glands, etc. Some studies have attempted to introduce these structures to construct 'assembloids'; however, these still lack structural similarities to the human eye or do not mature beyond primitive states [94,104]. Thus, the procurement of a fully integrated model of the human eye remains an important goal for the advancement of organoid models.

9. Conclusions

Human-induced pluripotent stem cell-derived ROs represent a definitive shift in ophthalmic research, moving away from the less representative animal models and moving towards a robust, patient-specific 3D system. By recapitulating disease-specific phenotypes and generating isogenic controls, these organoids provide an unprecedented view into elusive pathologies and the linkages between specific genes and retinal degeneration. They are ideal for modeling and are continually being analyzed with new chemical, functional, and histological parameters. Beyond their utility as discovery tools, ROs are foundational to the future of clinical translation. They offer a platform for high-throughput therapeutic screening and a self-renewing source of purified cells for transplantation in patients with IRDs.

The evolution from simple developmental models to these complex, multicellular systems marks a paradigm shift in our ability to address combat-related ocular trauma. The transition toward point-of-care diagnostic and therapeutic platforms represents the next frontier for military medicine.

While a fully engineered retina remains a long-term goal, the integration of vascular, immune, and neural components is making that vision increasingly feasible. Both individual and co-culture RO generation protocols are being evaluated and standardized, which can improve their efficiency and accessibility. Achieving this will solidify the RO platform as an indispensable tool in the fight against blinding diseases, leading directly to the implementation of personalized and curative strategies for both civilian and military populations.

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