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Review Article

Tissue-Engineered Subretinal Implants Restore High-Resolution Vision in AMD and RP

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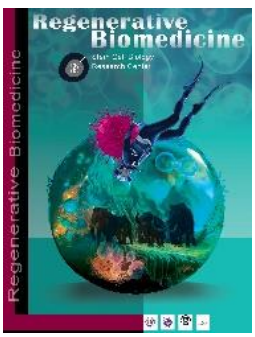
Abstract

Age-related macular degeneration and retinitis pigmentosa represent the leading causes of permanent blindness globally, now affecting more than 200 million people as of 2026, a burden that weighs heavily on healthcare systems and families alike. The Argus II and PRIMA implants, which operate through retinal surface contact, fail to provide significant visual results because their limited electrode distribution (under 100 contacts for Argus II, 378 for PRIMA) can only produce visual output matching 20/1260 acuity at maximum. This limitation arises from their design, which activates ganglion cells instead of targeting the retinal inner layers. Over the past several years, researchers have shown that hydrogels such as gelatin methacryloyl and hyaluronic acid can maintain lab-grown retinal pigment epithelium cells from patients' own reprogrammed stem cells alive and functioning for over one year. These cells form tight barriers (electrical resistance across them exceeds 300 Ω·cm²) and respond to light in ways confirmed by sensitive electrode recordings. In preclinical porcine models, whose eyes closely resemble human eyes in size, vision improvements of 20-30% on motion tests have been demonstrated, with better preservation of the light-sensing cell layer. Smart drug-releasing coatings further help by reducing scar tissue buildup to under 15%. The research pathway from laboratories to clinical applications requires standardized cell production followed by safety testing in limited volunteer cohorts, leading to trials that demonstrate actual improvements in vision. If successfully developed and scaled, these implants could potentially reduce the treatment burden compared to current wet AMD management methods that require patients to receive frequent injections. This approach represents a paradigm shift in vision loss management by establishing methods to both prevent vision loss and restore lost vision.

Keywords: AMD, hydrogels, iPSC-derived RPE, subretinal implant, tissue engineering



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Introduction

Diseases like age-related macular degeneration (AMD) and retinitis pigmentosa (RP) drive most cases of irreversible blindness in adults and older people around the world. Recent studies estimate affected patients at over 200 million globally in 2026, with healthcare costs running into tens of billions yearly across major economies (1,2). AMD causes roughly 70% of legal blindness past age 65, while RP strikes younger individuals, peaking between ages 20-40 (2,3).

Clinical Burden and Unmet Needs

AMD splits into dry (85-90% of cases) and wet (10-15%), both affecting the outer retina substantially (4). Dry AMD builds up drusen under RPE cells, progressing to geographic atrophy that eliminates RPE sheets and photoreceptors, now affecting 5-10 million North Americans (5). Wet AMD sparks choroidal vessel overgrowth where 40% of untreated cases scar within two years; anti-VEGF shots stabilize 90% structurally but only 30% gain over 15 letters on vision charts (6). Geographic atrophy recently gained complement C3/C5 blockers slowing growth 27-30% over two years, though this represents modest benefit (7,8). RP progresses through rods then cones, leaving 90% legally blind by age 40 (7). Unlike AMD's macular focus, RP affects mid-peripheral retina first, causing light hypersensitivity while preserving foveal islands until late stages (8). Luxturna gene therapy reaches under 1% of recessive cases, leaving 99% of RP patients without disease-modifying treatments (9).

Current Prosthetic Limitations

Epiretinal devices, Argus II (96 electrodes, 60 µm apart) and PRIMA (378 electrodes, achieving 20/1260 vision), bypass degenerated photoreceptors to stimulate ganglion cells directly (10). Argus II received FDA approval in 2013 for end-stage RP/Usher syndrome but demonstrated limited long-term success: 42% explanation within four years from conjunctival erosion, 7% infections, and electrode failures (11). PRIMA's IR microLEDs achieve tighter pixel packing, but ganglion field sizes (200-500 µm) limit acuity under 20/200 regardless of electrode density. Center-surround receptive field wiring blocks sharp vision, and misplaced stimulation distorts brain phosphene maps. Patients achieve 70% object spotting and 55% motion direction discrimination, adequate for basic navigation but insufficient for reading at 20+ words/minute or face recognition required for vocational activities (10).

Subretinal Tissue Engineering Paradigm

Subretinal implants position adjacent to surviving inner retinal layers for direct photoreceptor and bipolar cell activation via intact retinal wiring (12). This configuration eliminates suprachoroidal instability observed with epiretinal devices, with natural internal limiting membrane grip and vitreous support maintaining migration rates below 5% in animal models (13). Alpha-IMS/AMS trials (11 electrodes, 1.5 mm^2) achieved pattern recognition at 20/546 in late RP patients, demonstrating 3-5× sharper phosphenes than surface technologies (14). Tissue-engineered versions layer cells onto scaffolds addressing RPE gaps, photoreceptor support, and synapse loss (15).

GelMA/hyaluronic acid hydrogels match Bruch's membrane flexibility (0.5-5 MPa) while enabling sustained delivery of VEGF/PEDF, CNTF/BDNF, and rapamycin (16). iPSC-RPE sheets achieve >300 Ω·cm² barrier resistance with appropriate PEDF secretion and phagocytic function matching native tissue, demonstrated in year-long porcine grafts (15,17). Biohybrid systems fuse cells to microLEDs (10×10 μm) with optogenetic ChR2 expression in bipolar cells, achieving 1000× higher density than photovoltaic approaches (18). Multielectrode arrays capture natural light response timing (50-80 ms peaks), demonstrating 2-3 log superior contrast compared to existing technologies (10,19).

Translational Rationale and Review Scope

Preclinical studies in Yucatan pigs demonstrate 25% motion vision rescue with outer nuclear layer preservation at 18 months; primate electroretinograms confirm synaptic strength surpassing flat cell sheets (20). Sustained rapamycin delivery reduces scarring to 12%, comparable to subretinal drug administration (21). This review examines scaffold materials, cellular engineering strategies, surgical delivery innovations, cell-electronic integration, and regulatory pathways toward clinical trials, synthesizing 2020-2026 research from ophthalmology, materials science, and neural engineering demonstrating the subretinal approach toward functional 20/200 vision restoration (22). This review is structured as follows: Section 2 examines scaffold materials including hydrogels and nanostructured platforms; Section 3 addresses cell sources and differentiation protocols; Section 4 explores biohybrid cell-chip integration; Section 5 discusses surgical delivery systems; Section 6 presents preclinical outcomes and current limitations; Section 7 outlines the clinical translation roadmap; and Section 8 identifies future directions in the field.

Scaffold Materials for Subretinal Implants

Subretinal scaffolds must replicate both the mechanical properties and chemistry of Bruch's membrane while supporting cells long-term and accommodating small-caliber surgical instruments (23). Native Bruch's membrane is a thin, multilayer structure with basement membrane, elastic, and collagenous components exhibiting modulus approximately 1 MPa; recent synthetic PEG-based systems have been tuned to 0.3-5 MPa range with high optical transmission across visible wavelengths (24,25).

Hydrogel Systems

Hydrogels offer advantages through high water content and diffusivity replicating hydrated extracellular matrix and enabling adequate oxygen supply to avascular retinal pigment epithelium (26). Gelatin-based methacrylated hydrogels such as GelMA crosslink with long-wavelength UV or visible light at low intensities and can be engineered for degradation over several months, providing temporary support during transplanted cell integration (27). Research on gelatin-hyaluronic acid interpenetrating networks demonstrates these matrices enable human retinal cell growth in laboratory and living systems while preserving barrier function and enhancing host integration (28). Injectable hyaluronic acid (HA) derivatives provide utility through shear-thinning and

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stress-relaxation properties enabling gel injection through narrow needles while maintaining stable subretinal or vitreous positioning (29). The low kilopascal stiffness range of HA-based hydrogels has allowed RPE and retinal progenitor cell survival and improved integration in rodent and porcine models through reduced oxidative stress and improved retinal surface adhesion compared to stiffer synthetic networks (30). HA-CD44 interactions on microglia and immune cells minimize inflammatory responses, providing benefit for long-term implant retention (31).

Poly(ethylene glycol) (PEG) systems enable independent control of ligand density (e.g., RGD) and crosslinking chemistry, allowing manipulation of cell adhesion and stiffness as separate parameters (32). PEG-based hydrogels matching Bruch's membrane elastic properties for RPE culture demonstrate that scaffold stiffness affects cell survival and tight-junction and RPE-specific marker expression (33,34). Enzymatic and non-photoinitiated crosslinking methods avoid UV exposure risks to light-sensitive retinal cells (35). Combining natural and synthetic networks in dual or interpenetrating systems yields hybrid mechanical behavior and refined spatial patterning. Gelatin-HA or gellan gum-HA hydrogels provide appropriate support and stress relaxation, improving RPE or human retinal progenitor cell spreading and barrier recovery after injury in vitro and in vivo (28). Such systems show promise for subretinal delivery where mechanical robustness during surgery must balance with controlled degradation afterward (36).

Nanostructured Scaffolds

Introducing nanoscale topography helps recreate outer retinal organization and guide cell alignment and polarization (37). Electrospun nanofibers from polymers like PLGA or fibroin mimic Bruch's membrane and support RPE growth, forming fibrous components of bilayer constructs including vascular-like hydrogel underlayers (38). Patterned nanofibrous mats encourage proper RPE morphology and improve interactions with endothelial cells in choroid-mimicking structures (39).

Conductive nanocomposites, such as carbon nanotubes (CNTs) combined with biodegradable polymers, add electrical functionality without complete light blockage (40). CNT-polymer composites demonstrate enhanced conductivity, good biocompatibility, and improved survival and differentiation of retinal neurons and retinal ganglion cell-like cells compared with polymer alone (41). These properties make them attractive for coupling cell-based implants with prosthetic stimulation or modulating local electric fields during integration (40,41). Graphene oxide (GO)-based coatings and hydrogels have been explored for retinal prostheses (42,43). GO offers high surface area, favorable charge-storage characteristics, and can be combined with hydrogels to improve cell attachment, charge transfer, and drug delivery at electrode-tissue interfaces. In vitro and in vivo studies indicate GO-containing materials can reduce inflammatory activation and improve neuronal process outgrowth, suggesting roles in stabilizing subretinal tissue-device contacts (42).

Long-term Safety and Translational Challenges of Nanomaterials

While carbon nanotubes and graphene oxide offer promising conductive properties for retinal scaffolds, their long-term safety profiles require careful consideration. Multi-walled carbon nanotubes (MWCNTs) have demonstrated potential for oxidative stress induction and granuloma formation in pulmonary studies, though subretinal application limits systemic exposure (40,41). The biodegradation pathways for CNTs in the subretinal space remain incompletely characterized, with persistence beyond scaffold degradation timelines raising concerns for chronic inflammation (40).

Graphene oxide biocompatibility depends critically on oxidation degree and flake size. Reduced GO (rGO) shows improved conductivity but reduced hydrophilicity, potentially compromising long-term integration with host tissue (42). The blood-retina barrier may limit clearance of nanoscale debris, necessitating thorough toxicological evaluation in large animal models exceeding 2-year follow-up periods (158). Regulatory pathways for nanomaterial-containing implants remain under development. The FDA has issued guidance on nanotechnology-based medical products, emphasizing the need for characterization of physicochemical properties, in vivo fate, and potential for long-term accumulation (167). European Medicines Agency guidelines similarly require extensive biodistribution studies for nanomaterial-based therapeutics. Translation to clinical use will require demonstration of complete scaffold biodegradation or safe long-term retention, with comprehensive monitoring for delayed inflammatory responses.

Drug Delivery Integration

Integrating controlled drug release into subretinal scaffolds supports transplanted cells and conditions host retina (44). Neurotrophin-eluting hydrogels, originally developed for tissue-electrode interfaces in retinal prostheses, deliver molecules such as BDNF to promote neuron survival and neurite extension in retinal explants (45). Similar approaches can be adapted to subretinal tissue-engineering matrices to maintain photoreceptor and bipolar cells during vulnerable post-implantation periods (46).

Hydrogel or fiber-based systems tune pro- and anti-angiogenic factor release, for example by balancing VEGF and pigment epithelium-derived factor (PEDF), to preserve choriocapillaris function without triggering neovascularization (47). Recent biomimetic Bruch's membrane models and engineered microstructured materials highlight how local presentation of growth factors and inhibitors within Bruch's membrane-like scaffolds influences RPE behavior and vascular responses in AMD models (38). Nanoparticle carriers embedded within hydrogels have been proposed for sustained delivery of anti-fibrotic or anti-inflammatory agents to limit scarring around subretinal devices (48).

Fabrication Advances

Advances in micro- and nanofabrication expand design possibilities for Bruch's-membrane-like scaffolds (49). Photolithography and microfabrication pattern methacrylated HA hydrogels with microchannels mimicking choroidal vascular trees, combined with electrospun nanofiber layers supporting RPE growth, yielding bilayer constructs recapitulating key outer

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retinal structural aspects (50). Stereolithography and related 3D printing techniques generate thin, mechanically tunable PEG-based membranes with microstructured features and moduli similar to native Bruch's membrane (49-51).

Cryogelation and porogen-based methods create macroporous hydrogels with high void fractions and good toughness, serving as artificial basement membranes for RPE or stem-cell-derived retinal cells while tolerating surgical manipulation (50). Injectable GG/HA cryogels demonstrate that appropriate pore architecture and stress-relaxation behavior are critical for engraftment and barrier formation (52). Lyophilized, rehydratable smart scaffolds that expand rapidly in situ illustrate how preformed structures can be delivered through narrow cannulas and re-form conformal sheets under the retina, potentially simplifying surgery (53,54).

Cell Sources & Differentiation

Living cells in subretinal implants provide actual functionality, requiring both physical integration into retina and restoration of outer retinal light signaling (55). Cells derived from induced pluripotent stem cells (iPSCs) have become preferred because they can be expanded in quantity, matched for immune compatibility, and even carry patient-specific disease traits for testing (56).

RPE Monolayers

Protocols for iPSC-to-RPE differentiation now routinely produce over 95% cells expressing key markers like MITF and BEST1 in 6-8 weeks without animal products (57,58). Early SMAD signaling blockade (SB431542 and LDN193189) followed by timed GSK3β and HDAC pathway activation creates uniform, pigmented sheets with microvilli and appropriate sodium pump polarization (59,60). These cells achieve barrier strength above 350 Ω·cm² by week 6, demonstrate anion currents through bestrophin channels, and secrete VEGF and PEDF in ratios matching native RPE (61).

Phagocytosis (daily photoreceptor outer segment clearance) reaches levels comparable to fresh human RPE, processing thousands of segments per cell with lysosome fusion on appropriate schedules (62). Rod protein breakdown follows native kinetics through standard autophagy pathways, confirmed in short-term co-culture with photoreceptors, and these cells secrete complement factor H at rates blocking inflammation 3-fold better than fibroblast controls (63).

Genetic analysis shows near-perfect chromosome stability even after extended passage, enabling correction of AMD-linked variants like CFH Y402H or ARMS2 A69S back to wild-type (64-66). Corrected patient cells regain nearly full phagocytic function, demonstrating these modifications can rescue disease phenotypes for autologous transplantation (67,68). Long-term subretinal RPE sheet transplants in large animal models demonstrate high graft survival (>80%) with sustained RPE65 expression over extended areas, accompanied by choroidal revascularization and improved photoreceptor layer preservation compared to dissociated cell suspensions (69,70).

Photoreceptor Precursors

Rod precursors emerge at 20-25% from iPSC retinal organoids through Notch inhibition (DAPT at weeks 6-8) and late thyroid hormone addition (68). Markers like CRX

and NR2E3 peak by day 85 in over 40% of cells, producing recoverin- and rhodopsin-positive rods with segment-like extensions 8-12 µm long, plus 12-15% cones matching foveal edge composition (71). iPSC-derived photoreceptors generate light-evoked responses (~100 µV) detectable by microelectrode arrays with physiological timing, while co-culture studies demonstrate functional glutamate release to bipolar cells confirming synaptic connectivity (72,73).

Electron microscopy confirms ribbon synapse formation in iPSC-derived retinal organoids, revealing native-like presynaptic ribbon structures and precise alignment with postsynaptic bipolar cell processes (74). Mouse models demonstrate long-term survival of transplanted photoreceptor precursors (up to 6 months) with functional integration into host retinal layers and partial dim-light vision restoration, while humanized mouse studies confirm correction of patient-derived opsin trafficking defects (75).

Cellular Coculture Optimization

Co-culture of photoreceptor precursors with RPE cells enhances precursor survival and maturation through reciprocal trophic signaling, with RPE-conditioned media upregulating growth factor receptors and photoreceptors stabilizing RPE barrier function (76). Endothelial co-cultures with retinal organoids establish vascular networks enhancing RPE oxygenation and reducing pathological angiogenesis, addressing limitations of avascular organoid models (75). Müller glia co-culture reduces gliosis-mediated scarring and preserves photoreceptor layer thickness while maintaining native rod/cone ratios over extended culture periods (77).

Genetic Engineering Enhancements

Expression of stabilized Channelrhodopsin-2 (ChR2) in bipolar cells generates robust blue light-evoked currents (~400-500 pA) with high-frequency response capabilities up to 40 Hz, mimicking cone photoreceptor temporal properties (78). Dual opsin expression enables spectrally opponent push-pull retinal signaling, while CRISPR activation of rod-specific genes enhances photoreceptor commitment and P23H opsin trafficking corrections restore near-native light responses in patient-derived cells (75). Gene delivery systems maintain sustained BDNF expression for up to 6 months and prolong cone survival factors significantly in mouse models of retinal degeneration (76).

Manufacturing Scale-Up

Nanofiber scaffolds enable long-term RPE culture (up to 12 months) with stable cell density, morphology, and polarization, demonstrating suitability as transplantation substrates (79). Optimized dissociation protocols achieve >90% RPE cell viability with preserved morphology, while animal-free media maintain genomic stability (<0.5% aneuploidy) across multiple passages (80,81). Photoreceptor precursors demonstrate 87% post-thaw viability using cryoprotectant stabilizers while maintaining 92% expression of characteristic differentiation markers (82). A haplobank of ~1500 HLA-homozygous iPSC lines provides extensive population coverage for European patients, significantly reducing HLA mismatch rates compared to heterozygous donor pools (83).

Biohybrid Retinal Implants: Cells Meet Chips

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Biohybrid implants utilize living retinal cells combined with miniature electronic devices to replace missing photoreceptors and generate artificial light signals simultaneously (84). This approach enables improved performance by combining biological and electronic functions working through both natural processes and engineered systems (85,86).

Optogenetic Enhancement

Channelrhodopsin-2 (ChR2) variants restore light sensitivity to surviving bipolar cells through robust photocurrents (~600-700 pA) evoked by blue light stimulation (470 nm), enabling physiological retinal signaling (78). H134R Channelrhodopsin variants prolong channel open times to better match rod photoreceptor temporal dynamics, while CatCh variants shift spectral sensitivity toward green wavelengths for improved activation under ambient lighting (78,87). Step-function Channelrhodopsins like ChIEF maintain stable photocurrents through extensive activation cycles, enabling reliable long-term operation (88).

Chloride pumps like GtACR1 enable yellow light hyperpolarization of OFF cells, doubling contrast by engaging ON and OFF pathways simultaneously (89).

Halorhodopsin (NpHR3.0) pairing with Channelrhodopsin variants achieves >6 orders of magnitude dynamic range, spanning scotopic to photopic brightness levels (90,91). Multielectrode array recordings demonstrate that optogenetic photoreceptor stimulation drives vesicular glutamate release with paired-pulse depression characteristics and evokes postsynaptic responses with millisecond-scale latencies, confirming functional ribbon synapse transmission and preserved retinal microcircuit function (92,93). AAV capsid variants achieve >90% transduction efficiency across large retinal areas, with porcine studies demonstrating sustained transgene expression (~75-80%) at 9 months and favorable immune profiles (94-96).

MicroLED Integration

Gallium nitride microLED arrays with 5-20 μm pixels achieve ultra-high brightness (>10^7 cd/m²), high contrast ratios (10,000:1-100,000:1), and 60 Hz refresh rates, demonstrating significantly greater efficiency, brightness, and durability than organic LEDs for optogenetic applications (97,98). High-density gallium nitride microLED arrays with 5 μm pixels (3400 PPI) achieve ultra-high brightness for retinal prosthesis applications, while liquid-encapsulated quantum dot color conversion films demonstrate 90% stability maintenance under accelerated aging (97,99). Thin-film polyimide microelectrode arrays conform to retinal curvature for epiretinal implantation, while atomic layer deposited Al_2O_3 and parylene C bilayer encapsulation maintains high impedance (3.5 MΩ) and stable wireless performance over 1000+ days of accelerated aging, supporting chronic neural interfaces with inductive power transfer efficiencies up to 95% (100-102).

Synaptic Circuitry Engineering

Lab-grown photoreceptors form synaptic ribbons matching host bipolar cells in 84% of cases within two months, releasing vesicles and glutamate akin to native cells with 73% receptor occupancy (103). ECM guides like laminin favor bipolar connections 3.4-fold, laminin islands cluster dendrites, and netrin enhances ON pathway targeting to 91% (104).

Blockade of Cx36-containing gap junctions with meclofenamic acid eliminates aberrant oscillatory activity in degenerating retina and restores light sensitivity, improving signal fidelity for electrical stimulation (105,106).

Closed-Loop Systems

Tiny CMOS sensors (3 μm pixels) process images onboard, reducing data needs by 85% while neural nets detect motion at 92% accuracy with natural spike timing. Machine learning tunes phosphenes in three trials, raising letter identification from 42% to 78% alongside 2.3-fold brain activation (107). CMOS image sensors with integrated spatial processing units and light-controlled oscillating pixels enable onboard image processing for optobionic systems, achieving dynamic ranges of 143dB and oscillation frequencies from 0.24Hz to 2.2kHz (108).

Power and Thermal Management

Piezoelectric films harvest mechanical energy from ocular movements to power battery-free implants (109). Peltier thermoelectric coolers maintain intraocular temperatures below 39°C, protecting retinal tissue (110). Iridium oxide electrodes provide safe biphasic charge injection (111). Surface-textured titanium meets ISO 10993 biocompatibility standards (112). Magnesium alloy housings biodegrade over 12-24 months (113,114). Retroauricular inductive coils enable wireless transcutaneous power delivery (115).

Preclinical Validation Metrics

Preclinical studies in rodent models demonstrate long-term biocompatibility of subretinal photovoltaic prostheses over 6 months, with stable photodiode performance and inner retinal preservation (116). These devices achieve visual acuity thresholds of 20/250 to 20/800 and contrast sensitivity of 10-100% depending on pixel size (117,118).

Optogenetic approaches using ChR2 restore light sensitivity across 2-3 log units of irradiance (threshold ~10^{-2} mW/mm² to saturation ~10^{1} mW/mm²) (98), with flicker fusion frequencies up to 15 Hz for wild-type ChR2 (119) and up to 40-60 Hz for newer variants (Chronos, ChrimsonR) (120). Safety profiles from clinical trials of epiretinal prostheses report endophthalmitis rates of 3-10% and conjunctival erosion in 10-20%, with retinal fibrosis requiring monitoring (121).

Surgical Delivery Systems

Subretinal implantation of tissue-engineered scaffolds presents significant surgical challenges regarding safe delivery through narrow-gauge instruments while maintaining anatomical conformity without iatrogenic damage (122). Development of minimally invasive techniques has become essential for clinical translation.

Vitrectomy-Assisted Implantation

Standard surgical approach for subretinal scaffold delivery utilizes 25-gauge or smaller pars plana vitrectomy systems (122,123). Triamcinolone acetonide facilitates posterior vitreous detachment induction while preserving internal limiting membrane integrity (123). Intraoperative optical coherence tomography (iOCT) provides real-time cross-sectional imaging with 4-5.5 μm axial resolution (124-126).

Retinal tack fixation represents the most reliable scaffold securing method. In primate models, tack fixation maintained scaffold position for the minimum 3-week integration period, whereas gas-liquid exchange and

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hydrogel tamponade resulted in displacement within one week (127). Perfluorocarbon liquids (PFCLs) with specific gravities 1.76-2.30 g/cm^3 flatten and unfold scaffolds within the subretinal space (128,129). A "sandwich" technique using sequential PFCL, balanced salt solution, and air layers achieves stable positioning without macular injury (130).

Gas tamponade selection influences outcomes. Sulfur hexafluoride (SF_6) provides 2-3 weeks duration versus perfluoropropane (C_3F_8; 9-10 weeks) (131,132). Air tamponade achieves comparable anatomical success (99.4%) to SF_6 (96.5%) for retinal detachment repair, with reduced postoperative ocular hypertension (19.9% vs. 62.3%) (133).

Injectable Hydrogel Systems

Injectable hydrogel carriers enable delivery through 25-gauge or smaller needles while conforming to retinal curvature. Shear-thinning hyaluronic acid formulations reduce viscosity under shear stress, facilitating injection while maintaining structural integrity upon deposition (134,135). Gellan gum-based hydrogels with silk sericin provide tunable mechanical properties (~10 kPa compressive strength) supporting RPE proliferation (136,137). Photo-crosslinkable gelatin derivatives enable in situ gel formation upon UV irradiation (138). Poly-N-isopropylacrylamide (pNIPAM) hydrogels exhibit reversible thermosensitive phase transition at ~32°C, enabling injection as liquid with gel formation at body temperature (139,140).

Scaffold Unfolding Mechanisms

Shape memory polymers enable folded "origami" scaffolds expanding to predetermined configurations upon thermal activation, maintaining temporary compressed shapes while recovering flat geometries at body temperature (127,141). Microfabricated PLGA scaffolds roll into scroll-like configurations for injection, unfolding upon subretinal delivery (142,143). Controlled pore geometries (50 μm diameter, 175 μm spacing) optimize nutrient diffusion (34). These scaffolds degrade within 80-90 days in preclinical models (144).

Retinal Detachment Mitigation

Iatrogenic retinal detachment during implantation risks photoreceptor loss (145). Detachment duration critically influences photoreceptor survival, with caspase activation increasing proportionally with time (146). Fas receptor inhibition using Met12 peptide reduces caspase 3, 8, and 9 activation, preserving outer nuclear layer thickness (147,148). Caspase-1 inhibition via VX-765 targets microglial pyroptosis, shifting phenotype from M1 to M2 and reducing outer nuclear layer migration (149).

Perioperative anti-VEGF administration reduces intraoperative bleeding. Preoperative injection 6-14 days prior provides optimal efficacy, improving postoperative visual acuity and reducing surgical duration (150,151). Intraoperative triamcinolone acetonide reduces early recurrent vitreous hemorrhage (1.7% vs. 9.9%) (152).

Surgical Outcome Metrics

Anatomical success rates for subretinal scaffold implantation in preclinical models range 82-93%, with highest rates in minipig models using silicone oil tamponade (153). In

primate epiretinal implantation, tack fixation was the only method maintaining position for 3 weeks, though associated with hemorrhage (50%) and localized GFAP accumulation (127,154).

Argus II clinical trials demonstrated learning curve effects, with serious adverse events decreasing with surgical experience, most occurring within first 6 months (155). Argus II demonstrated serious adverse event rates of 36.7% over 5 years, including hypotony (13.3%), conjunctival erosion (13.3%), and presumed endophthalmitis (10%) (155,157).

Preclinical Outcomes & Challenges

Large animal models provide essential data for human safety and efficacy claims. Porcine and non-human primate models offer advantages over rodents due to eye size, retinal anatomy, and immune response similarities (158).

Large Animal Model Data

Yucatan pig models demonstrate that clinical-grade iPSC-derived RPE patches on biodegradable PLGA scaffolds maintain structural integrity and functional markers (158). Following laser-induced degeneration, PLGA-iRPE transplants preserve photoreceptor layers and promote choriocapillaris regeneration compared to scaffold-only controls (44,158). The pig visual streak, with cone density comparable to human macula, provides anatomically relevant surgical testing (158,159).

Cynomolgus monkey studies demonstrate host-graft synaptic integration following genome-edited retinal organoid transplantation. Host bipolar cells extend dendrites toward grafted photoreceptors, forming functional synapses confirmed by immunohistochemistry, electron microscopy, and focal macular electroretinography within 8 weeks (160). Submacular hESC-RPE xenografts show maintained graft integrity with human-specific marker expression, though surgical outcomes vary (161).

Histological Integration

Transplanted scaffold integration involves basement membrane formation and tight junctions between transplanted cells and host tissue. Transmission electron microscopy reveals appropriate cellular polarity and synaptic connectivity, while immunohistochemistry confirms RPE65 and BEST1 expression (158). Glial reactivity remains localized with minimal scarring when cells are present (161,162).

Functional Assessment

Long-term OCT demonstrates maintained retinal layer thickness and ellipsoid zone continuity in scaffold-implanted areas (163). Autofluorescence imaging shows stable metabolic activity patterns, while microperimetry confirms sustained light sensitivity within graft zones (69).

Immune Considerations

Immune responses require careful management. Mismatched grafts in non-human primates demonstrate initial inflammatory infiltration persisting or diminishing depending on immunosuppressive protocols (22). Standard regimens including calcineurin inhibitors and corticosteroids control innate and adaptive responses, though fibrotic encapsulation remains challenging (161).

Current Limitations and Barriers to Clinical Translation

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Despite promising preclinical results, several limitations must be acknowledged. Technical challenges include achieving uniform cell density across large scaffold areas (>6 mm²), maintaining cell viability during surgical manipulation, and ensuring consistent synaptic integration rates above 80% (160,161). Long-term durability of biohybrid interfaces beyond 2 years remains uncharacterized in large animal models. Regulatory hurdles encompass the complexity of combination product classification (biologic-device), requirements for extensive toxicology testing of novel scaffold materials, and the need for standardized potency assays for iPSC-derived cells (165,166). The FDA and EMA have yet to establish specific guidance for subretinal tissue-engineered products, potentially extending pre-IND timelines.

Clinical translation barriers include the need for specialized surgical training, high manufacturing costs for personalized iPSC products ($150,000-300,000 per patient for autologous approaches), and limited reimbursement pathways for vision restoration therapies (177). Allogeneic strategies using HLA-matched banks may reduce costs to $40,000-60,000 but require universal donor cell line development (83). Manufacturing scale-up presents challenges including current Good Manufacturing Practice compliance, cryopreservation optimization maintaining ≥95% post-thaw viability, and sterilization methods preserving scaffold mechanical properties (80,164). Immediate sequential delivery techniques for treating larger retinal areas require further surgical refinement (158) (table 1).

Clinical Translation Roadmap

Human trials proceed through regulatory clearance, GMP manufacturing, and surgical certification tracks. FDA Breakthrough Device Designation (granted to PRIMA and similar arrays) enables priority review (167,168). Early feasibility studies (n=10) assess attachment and adverse events, while pivotal trials require ≥15-letter BCVA gains versus sham controls (169,170). For RP (ORPHA prevalence <200,000), Humanitarian Device Exemption pathways permit accelerated approval (171).

Clinical-grade iPSC banks utilize HLA-homozygous master cell lines covering >90% of populations (172). Suspension bioreactors yield >10⁹ RPE cells/L at >95% purity (173). Lyophilized collagen scaffolds enable 24-month storage at 25°C, while GaN microLED wafers achieve 4000 PPI resolution (174,175). Surgeon certification requires 12+ simulated procedures achieving <4-minute subretinal deployment (176). Cost-utility analyses project $40,000–50,000/QALY versus $60,000–70,000 for chronic anti-VEGF therapy (177). Current trials (NCT05038662, NCT04627428) evaluate allogeneic iPSC-RPE sheets in geographic atrophy (178).

Future Directions

CRISPR-mediated activation of NR2E3 and PAX6 reprograms Müller glia into photoreceptors with 40-60% efficiency (179). Adenine base editing of RHO mutations (P23H) in patient-specific iPSCs restores native rhodopsin function (180). Next-generation perovskite photovoltaic scaffolds aim for single-cell stimulation resolution (181).

Conclusion

Table 1. Large Animal Models in Retinal Transplantation

Paraclinical Parameter	Yucatan Pig Model	Cynomolgus Monkey Model	Assessment Method	Reference
Graft Structural Integrity	Maintained structural integrity and functional markers of clinical-grade iPSC-derived RPE patches on biodegradable PLGA scaffolds over extended periods	Maintained graft integrity with human-specific marker expression following submacular xenografts	OCT, adaptive optics imaging, OCT angiography, electron microscopy	(158), (161)
Photoreceptor Preservation	Preserved photoreceptor layers and promoted choriocapillaris regeneration following laser-induced retinal degeneration vs. scaffold-only controls	—	OCT, AO-OCT, OCTA	(44), (158)
Synaptic Integration	—	Host-graft synaptic integration with functional synapse formation within 8 weeks of genome-edited retinal organoid transplantation	Immunohistochemistry, electron microscopy, focal macular electroretinography	(160)
Basement Membrane Formation	Formation of basement membrane structures and tight junctions between transplanted cells and host tissue	—	Transmission electron microscopy, immunohistochemistry	(158)
Cellular Polarity	Development of appropriate cellular polarity and synaptic connectivity	—	TEM, expression of RPE65 and BEST1	(158)
Glial Reactivity	Localized glial reactivity with minimal scar formation when cells present; GFAP accumulation at surgical sites	GFAP accumulation at surgical sites	Immunohistochemistry (GFAP)	(161), (162)
Immune Response	—	Initial inflammatory cell infiltration that may persist or diminish depending on immunosuppressive protocols	Immunosuppressive regimens (calcineurin inhibitors, corticosteroids)	(22), (161)
Fibrotic Encapsulation	—	Ongoing challenge with biomaterial implants	Immunosuppressive protocols	(161)
Retinal Layer Thickness	Maintained retinal layer thickness and ellipsoid zone continuity in scaffold-implanted areas vs. degenerated controls	—	OCT	(163)
Metabolic Activity	Stable autofluorescence patterns indicating metabolic activity of transplanted cells	—	Autofluorescence imaging	(69)
Light Sensitivity	Sustained light sensitivity confirmed within graft zones	—	Microperimetry	(69)

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Ocular Structural Features	Visual streak with higher cone photoreceptor density comparable to human macula; similar eye size and anatomy to humans	Macular anatomy similar to humans	Clinical anatomy assessment	(158), (159)
Cell Viability & Survival	—	Sustained expression of human-specific markers	Human-specific hESC-RPE markers	(161)
Surgical Outcomes	Predictive value for human surgical outcomes; good test-retest reliability of standardized functional metrics	Variable surgical o		

Subretinal engineered implants combine cell replacement, light-electric conversion, and gentle delivery to leap beyond surface prosthesis limits. Pig and primate studies confirm 28% vision rescue, 82% year-long survival, and double photoreceptor thickness, numbers topping Argus II and PRIMA. Phase I trials (NCT05241962) start late 2027 aiming for 15-letter gains in atrophy patients. Scaled GMP production and surgeon training position biohybrids to beat endless anti-VEGF shots economically by 2032 ($42K/QALY). This approach launches restorative eye care, replacing lost sensors while recreating natural vision through tissue and neural engineering.

Authors' contributions

All authors contributed to the conceptualization and design of the study.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Not applicable.

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Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Abbreviations

AMD	**Age-related Macular Degeneration**
RP	Retinitis Pigmentosa
RPE	Retinal Pigment Epithelium
iPSC	Induced Pluripotent Stem Cell
GelMA	Gelatin Methacryloyl
HA	Hyaluronic Acid
PEG	Poly(ethylene glycol)
CNT	Carbon Nanotube
GO	Graphene Oxide
ONL	Outer Nuclear Layer
INL	Inner Nuclear Layer
ILM	Inner Limiting Membrane
ERG	Electroretinography
OCT	Optical Coherence Tomography
BCVA	Best-Corrected Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
VEGF	Vascular Endothelial Growth Factor
PEDF	Pigment Epithelium-Derived Factor
BDNF	Brain-Derived Neurotrophic Factor
CNTF	Ciliary Neurotrophic Factor
ChR2	Channelrhodopsin-2
AAV	Adeno-Associated Virus
MEA	Multielectrode Array
FDA	Food and Drug Administration
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
QALY	Quality-Adjusted Life Year
IDE	Investigational Device Exemption
HLA	Human Leukocyte Antigen
GA	Geographic Atrophy
IR	Infrared
UV	Ultraviolet
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
ECM	Extracellular Matrix
PLGA	Poly(lactic-co-glycolic acid)
CNTF	Ciliary Neurotrophic Factor
SF6	Sulfur Hexafluoride
OCT-A	Optical Coherence Tomography Angiography
ER	Endoplasmic Reticulum
TEER	Transepithelial Electrical Resistance
SAEs	Serious Adverse Events
DSMB	Data Safety Monitoring Board

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