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Cell-based regenerative therapy for retinal diseases: challenges and emerging bioengineering strategies

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ABSTRACT

Cell-based regenerative therapy holds promise for a broad spectrum of retinal diseases characterized by irreversible photoreceptor cell (PRC) loss, including retinitis pigmentosa (RP) and age-related macular degeneration. While gene therapy has delivered landmark successes for selected indications, it does not directly replace lost PRCs and is not well suited for advanced-stages of diseases. In this context, cell-based regenerative approaches—either PRC suspensions or retinal sheets—aim to rebuild the outer retinal circuitry and restore light responses across different retinal diseases. In addition to its relatively high prevalence (1 in 3000–5000 individuals), the PRC-specific degeneration pattern in RP has motivated numerous preclinical studies aimed at clinical application. In this review, we first outline the two major graft modalities—cell suspensions and retinal sheet transplantation—from the perspective of their respective advantages and limitations. Here, we summarize preclinical and clinical evidence for both modalities, highlighting the first-in-human trial of transplantation of human iPSC–derived retinal organoid sheets in late-stage RP, which demonstrated a favorable safety profile and two-year graft survival. We then analyze the challenges that emerged from this first-in-human trial and discuss potential bioengineering and biological solutions. Finally, we consider the prospects of extending these transplantation strategies beyond RP to macular diseases, where PRC replacement may also provide therapeutic benefit. Collectively, the field is transitioning from proof-of-concept to diversified clinical exploration; converging advances in developmental biology, genome engineering, and high-throughput cell analytics are poised to accelerate functional vision restoration in retinal diseases.

1. Introduction

Irreversible loss of photoreceptor cells (PRCs) represents a final common pathway leading to blindness in many retinal diseases, including retinitis pigmentosa (RP) and age-related macular degeneration. Among them, RP is a clinically and genetically heterogeneous inherited retinal dystrophy characterized by progressive PRC-specific degeneration, leading to night blindness, peripheral field loss, and eventual central vision decline. Affecting 1 in 3000–5000 individuals and linked to more than 80 non-syndromic genes plus additional loci in syndromic forms (RetNet; https://sph.uth.edu/retnet/) [1], RP remains a leading cause of inherited retinal blindness in adults and a major unmet medical need in developed countries. Over the past decade, gene therapy strategies have achieved landmark successes in selected genotypes of inherited retinal disease— most notably in biallelic RPE65-mediated RP, where gene therapy demonstrated clinically

Abbreviations: BCs, bipolar cells; ESC, embryonic stem cell; FACS, fluorescence-activated cell sorting; iPSC, induced pluripotent stem cell; MACS, magnetic-activated cell sorting; MH, macular hole; NHP, non-human primate; OCT, optical coherence tomography; ONL, outer nuclear layer; POSs, photoreceptor outer segments; PRC, photoreceptor cell; RGC, retinal ganglion cell; RO, retinal organoid; RPC, retinal progenitor cell; RPE, retinal pigment epithelium; RP, retinitis pigmentosa; SAG, smoothened agonist.

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Table 1
Advantages and disadvantages of graft formulation in transplantation.

Graft formulation	Advantage	Disadvantage
PRC Suspension	• Purified photoreceptor cells Possible host-graft synaptic integration • Adjustable graft cell amount • Simple and less invasive procedure	• Poor short-term survival rate • Unstable long-term engraftment • Impaired outer segment formation
Retinal Sheet	• Stable long-term engraftment • Robust maturation of the photoreceptor Stable formation of outer segments • Low immunogenicity • Potential preservation of the graft lamination	• Un-purified photoreceptor cells Potential inhibition of host–graft integration • Complex and invasive procedure

PRC, photoreceptor cell.

meaningful improvements in functional vision [2]. Nevertheless, gene therapy does not directly replace PRCs that are already lost, and thus may be poorly suited to eyes with advanced RP where the outer nuclear layer (ONL) is profoundly thinned or absent. This therapeutic gap motivates cell-based regenerative approaches aimed at rebuilding outer retinal circuitry.

For cell-based therapy, two principal cellular modalities have emerged: (i) subretinal cell suspensions (often purified PRCs) and (ii) three-dimensional retinal sheets that preserve retinal laminar structures also containing other retinal cells than PRCs. Both strategies have shown preclinical evidence of maturation of graft PRCs, graft–host synapse formation, and improvements in electrophysiology and visually guided behavior [3–7]. Based on these preclinical studies, a first-in-human trial of subretinal transplantation of human induced pluripotent stem cell (iPSC)-derived retinal organoid (RO) sheets in patients with late-stage RP reported a favorable safety profile and survival of the grafts for two years, supported by multimodal imaging, thereby providing an initial clinical application for retinal sheet grafts [8].

Despite these encouraging results, two fundamental challenges remain in cell-based regenerative therapy for retinal diseases. The first is how to enrich graft-appropriate cell populations from ROs. The second is how to promote robust synaptic connections between donor PRCs and host bipolar cells. This narrative review focuses on cell-based regenerative strategies for advanced RP and their potential extension to macular diseases, emphasizing (i) the characteristics of two major graft modalities—PRC suspensions and retinal sheets; (ii) the current state and challenges of clinical translation as highlighted by the first-in-human trial of retinal sheet transplantation; (iii) emerging bioengineering solutions aimed at label-free enrichment technologies and genetic modification to improve graft–host synaptic connections; and (iv) the prospects for expanding indications to macular diseases.

2. Cell-based strategies: graft modalities

Research on PRC transplantation for RP model animals can be traced back more than two decades [9,10]. Clinical research on PRC transplantation for patients with RP was conducted around the same time, with early studies reporting transplantation of fetal retinal cell suspensions as well as retinal sheets combined with retinal pigment epithelium (RPE) [11–13]. In a long-term safety study of subretinal fetal neuroretinal cell suspensions, no clinical evidence of rejection was observed up to 12–40 months after transplantation [11]. For retinal sheets, case series and a phase II study reported survival without apparent clinical rejection and visual acuity gains in a subset of patients over 5 years [12,13]. However, a lack of evidence for host–graft synaptic restoration, ethical concerns, and limited availability of donor fetal tissue prevented wider clinical adoption.

Early landmark work on host–graft synaptic integration came from MacLaren et al., who transplanted early postnatal GFP-labeled PRC suspensions into the ONL of adult murine retinas that retained host PRCs, demonstrating synapse formation and apparent functional recovery [14]. Subsequent studies using rod PRC precursors [15,16] or cone PRC precursors [17] reported similar outcomes. However, later investigations revealed that the observed recovery effects were not primarily due to genuine host–graft integration, but rather to cytoplasmic material transfer. In this process, proteins such as GFP were transferred from donor to host PRCs, resulting in host PRCs appearing GFP-positive and giving the impression of functional recovery without true synaptic connectivity [18–20]. Since then, the field has converged on the consensus that functional rescue must be evaluated in late-stage degeneration models with complete loss of the ONL, thereby minimizing the confounding influence of material transfer [3,4].

In parallel, a major paradigm shift occurred with the advent of stem cell technologies. The pioneering work by Sasai et al. on embryonic stem cell (ESC)–derived ROs [21], together with the establishment of iPSC technology by Yamanaka et al. [22], opened new avenues for cell-based regenerative therapy and sparked global research efforts using ESC/iPSC-derived ROs [23–25]. Alongside these advances, two principal graft modalities have emerged—PRC suspensions and retinal sheet transplantation—each with distinct advantages and limitations, which will be reviewed in the following sections (Table 1).

2.1. Photoreceptor cell suspension modalities (Table 2)

PRC suspension transplantation offers several advantages (Table 1). First, it allows for the use of purified PRCs, thereby enabling supplementation of the specific PRC types that are lost in disease. Second, the number of grafted cells can be readily adjusted by varying the cell suspension concentration. Third, the surgical procedure itself is relatively simple compared with sheet transplantation, which may also enable the coverage of a large area. In addition, because the transplanted PRCs are not pre-connected to secondary neurons, they are theoretically more likely to form synapses with host bipolar cells (BCs).

Despite these advantages, several disadvantages have been reported (Table 1). Suspension grafts typically show low survival rates [26], and stable long-term engraftment is difficult to achieve [27]. In addition, because supporting cells such as Müller glia are not included in the suspension, graft PRCs often fail to align properly, resulting in poorly developed PRCouter segments (POSs) [27] unless the cells integrate in the remaining host ONL[28]. It has been reported that the survival rate of human PRC precursor suspensions remained at approximately 6 % three weeks after transplantation in rodent models with immunosuppression [26], and non-human primate (NHP) models have also shown a lack of stable long-term engraftment at the graft site [27]. In parallel, studies of combinatorial constructs—pairing purified PRCs with artificial scaffolds or RPE sheets—have been conducted [29], with the primary aim of enhancing graft survival [30], promoting PRC polarity [31], and re-establishing physiological PRC–RPE interactions [32]. Although based on suspension-derived PRCs, these approaches are conceptually closer to sheet transplantation modalities discussed in the next section.

In practice, transplantation suspensions are typically prepared from dissociated human ESC/iPSC-derived ROs, with PRCs enriched using fluorescence-activated or magnetic-activated cell sorting (FACS or MACS). While preclinical studies have commonly relied on PRC-reporter

Table 2
Proof-of-concept studies of PRC suspension transplantation cited in this review.

Cell types (graft)	Recipient Animals	Findings	Reference
• Human fetal retinal cells (14–18 weeks' gestational age)	• Patients with advanced RP (n = 14)	Long-term safety (12–40 months after transplantation) No clinical appearance of detrimental effects after transplantation	Das et al. [11]
• Retinal microaggregate suspension from P13 Wild-type mice	• C3H/HeJ (rd/rd) mice: P13	1 Graft maturation: light and transmission EM (graft-derived POS development) 3 Light signal transmission to host RGCs: 33–35 days after transplantation Electroretinograms and RGC responses using a differential bipolar surface electrode.	Radner et al. [9]
• Nrl-GFP rod PRC precursors from P1 mouse	• Wild-type mice • RD mice (rd, rds, rho−/−): 6–12 weeks old	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic protein (Bassoon)] 3 Light signal transmission to host RGCs: Dark-adapted microelectrode recordings, Pupillary light reflex sensitivity	MacLaren et al. [14]
• Nrl-GFP rod PRC precursors from P4-8 mice	• Gnat1−/− mice: 6–8 weeks old * Assessed 4–6 weeks after transplantation	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic proteins (CtBP2 and Bassoon) and Dystrophin] and EM 3 Light signal transmission to host RGCs: Intrinsic Signal Optical Imaging 4 Improvement in behavioral tests of vision: Optokinetic head tracking and visually guided water-maze test	Pearson et al. [15]
• Tg (Nrl-L-EGFP) rod PRC precursors from P3-4 mice	• C3H/HeNHsd (rd1) mice: 10–12 weeks old • Tg (CAG-DsRed*MST)1/Nagy/J mice (rd1 background): 10–12 weeks old	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic proteins (Synaptophysin and Bassoon)] 3 Light signal transmission to host retina: Pupil light response test 4 Improvement in behavioral tests of vision: Light-mediated behavior test	Singh et al. [16]
• Rho-GFP mESC-derived PRC precursors (DD29)	• Gnat1-/mice: 8–12 weeks old • Rho−/− mice: 3–4 weeks old • Prph2rd2/rd2 mice: 8 weeks old	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic protein (CtBP2 and Dystrophin)] (3. Ex vivo Ca2+ imaging: PRCs responses)	Gonzalez-Cordero et al. [23]
• Tg (Nrl−/−;actinGFP) cone-rich PRC precursors from P1-8 mice	• Wild-type mice (C57BL/6 J): 3–6 weeks old • Nrl−/− mice: 3–6 weeks old • Cpfl1 mutant mice: 3–6 weeks old	1 Graft maturation: IHC (Cone-POS development) and CLEM (correlative light and EM) 2 Host-graft synapse formation: IHC [presynaptic proteins (Synaptophysin and Bassoon)] 3 Light signal transmission to host RGCs: Microelectrode arrays	Santos-Ferreira et al. [17]
• H9 hESC-derived PRC precursors • HA hiPSC-derived PRC precursors	• Wild-type mice • C3H/HeNHsd-Pde6brd1 (rd1) mice: 10–12 weeks old * Immunosuppresed with cyclosporine	1 Graft maturation: IHC (Rod- and Cone-POS development) 2 Host-graft synapse formation: IHC [Presynaptic protein (Synaptophysin)] 4 Improvement in behavioral tests of vision: 1) Optomotor response and 2) Light avoidance response	Barnea-Cramer et al. [26]
• Crx-GFP mESC-derived cone PRCs (DD26)	• Wild-type mice • Aipl1−/− mice: 8 weeks old *Assessed 3 weeks after transplantation	1 Graft maturation: IHC (Rod and Cone-PRCs, * POS was indistinct) 2 Host-graft synapse formation: IHC [Presynaptic protein (CtBP2 and Synaptophysin)]	Kruczek et al. [3]
• CRX+/tdTomato hESC(H9)-derived-PRC precursors (DD74-106)	• Cynomolgus monkeys (*wild-type and **laser-induced RD model) * Assessed for 29–41 weeks after surgery (n = 2) ** Assessed for 5–12 weeks after surgery (n = 3)	1 Graft maturation: IHC (Cone-PRCs, * POS was indistinct) 2 Host-graft synapse formation: IHC [Presynaptic protein (Synaptophysin)] * OCT and FAOSLO revealed tdTomato-positive aggregates resembling rosette-like structures in vivo.	Aboualizadeh et al. [27]
• H9 hESC-derived cone-PRC precursors • CNGB3 mutant hiPSC-derived cone-PRC precursors * Purified by L/M-opsin-GFP (17 ± 2 weeks old)	• rd1/Foxn1nu mice: 3 months (11–14 weeks) old * Assessed 3–4 months after transplantation	1 Graft maturation: IHC (Cone-POS development) and TEM (Transmission EM) 2 Host-graft synapse formation: IHC [presynaptic (CtBP2 and Synaptophysin) and postsynaptic proteins (mGluR6)] and TEM 3 Light signal transmission to host RGCs: Microelectroretinograms and Multielectrode Arrays 4 Improvement in behavioral tests of vision: Light avoidance assay	Ribeiro et al. [6]

Numbers (1–4) in the "Findings" column indicate the primary levels of proof-of-concept demonstrated in each study: (1) graft maturation (POS development); (2) host–graft synapse formation; (3) light signal transmission to host RGCs; and (4) improvement in behavioral tests of vision.
DD, differentiation day; EM, electron microscope; ESC, embryonic stem cell; GFP, Green Fluorescent Protein; IHC, immunohistochemistry; iPSC, induced pluripotent stem cell; POS, photoreceptor outer segment; PRC, photoreceptor cell; RGC, retinal ganglion cell; RD, retinal degeneration; RP, retinitis pigmentosa.

Table 3
Proof-of-concept studies of retinal sheet transplantation cited in this review.

Cell types (graft)	Recipient Animals	Findings	Reference
• Human fetal retina with RPE (13 weeks' gestational age)	• One Patient with advanced RP	4 Improvements in BCVA at 1 year after transplantation No rejection of the implanted tissue (* The pigmentation of the graft lost) * Multifocal electroretinogram showed no clear signal pre- and post-operatively.	Radtke et al. [12]
• Rat fetal retina (E19-E20) with RPE from Long-Evans rat	• RCS nude rats: P37-69	1 Graft maturation: IHC (S-antigen–positive cells, * POS tended to be short or absent) 3 Light signal transmission to cortex: Superior Colliculus Electrophysiology 63 days to 10 months after transplantation	Woch et al. [10]
• Human fetal retina with RPE (10–15 weeks' gestational age)	• Patients with advanced RP (and AMD): 6 eyes (and 4 eyes)	Long-term follow-up (1–6 years) 4 Improvements in BCVA (3/10 eyes) and microperimetry (* Only one patient data) No rejection of the implanted tissue	Radtke et al. [13]
• Rx:GFP mESC- derived RO (DD11-24) • Nrl:GFP miPSC-derived RO (DD11-24)	• rd1 mice: 6–8 weeks old *assesed 2 weeks to 6 months after transplantation	1 Graft maturation: IHC (Rod-POS development) and EM 2 Host-graft synapse formation: IHC [presynaptic proteins (CtBP2)]	Assawachananont et al. [24]
• Rx:Venus hESC (KhES-1)-derived RO (DD60) • Crx:Venus hESC (KhES-1)-derived RO (DD60)	• SD-Foxn1 Tg (S334ter)3Lav nude rats: 6–8 weeks old • cynomolgus and rhesus monkeys (injury induced RD models)	1 Graft maturation: IHC (Rod-POS development) and EM in Rats, IHC (Rod-/cone-POS development) in NHPs 2 Host-graft synapse formation: IHC [presynaptic proteins (CtBP2) in NHPs] * Focal electroretinogram: a- and b-waves were almost nonrecordable in NHPs	Shirai et al. [33]
• Nrl-GFP miPSC-derived RO (DD13-14) • Nrl-GFP/ROSA::NRl-CtBP2-tdTomato miPSC-derived RO (DD13)	• Tg (Pcp2-EGFP)2Yuza/rd1-2 J (L7-GFP/rd1) mice 7 or more weeks old	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic (CtBP2) and post-synaptic (CaV1.1) proteins] 3 Light signal transmission to host RGCs: Micro-electroretinography 4 Improvement in behavioral tests of vision: Shuttle Avoidance System Test	Mandai et al. [4]
• CSC14 (NIH 0284) hESC-derived RO (DD30-65)	• SD-Foxn1 Tg (S334ter)3Lav nude rat: P26-38	1 Graft maturation: IHC (Rod/Cone-POS development) 2 Host-graft synapse formation: IHC [presynaptic proteins (Synaptophysin and Bassoon)] 3 Light signal transmission to cortex: Superior Colliculus Electrophysiology 4 Improvement in behavioral tests of vision: Optokinetic Response Testing	McLelland et al. [25]
• 1231A3 hiPSC-derived RO (DD60)	• SD-Foxn1 Tg (S334ter)3Lav nude rats: 2–5 months old • Laser-induced RD model NHPs (cynomolgus/rhesus monkey)	Long-term follow-up (5 months in rats and 2 years in NHPs) 1 Graft maturation: IHC (Rod/Cone-POS development) 2 Host-graft synapse formation: IHC [presynaptic proteins (CtBP2) and gap junction marker (Cx36)] 3 Light signal transmission to host RGCs: Multi-electrode array recording for Rats	Tu et al. [5]

(*continued on next page*)

Table 3 (*continued*)

Cell types (graft)	Recipient Animals	Findings	Reference
		4 Improvement in behavioral tests of vision: Visually-guided saccade tests for NHPs	
Wild -type and genome edited ROs (Bhlhb4−/−, and Islet 1−/−) • Tg (Nrl-GFP) miPSC-derived RO (DD10-15) • Nrl-GFP/ROSA::NRl-CtBP2-tdTomato mESC-derived RO (DD10-15)	• rd1 mice: 8–12 weeks old • rd1; L7-GFP mice: 8–12 weeks old • rd1; Thy1-GCaMP3 mice: 8–12 weeks old (Ca^{2+} imaging)	1 Graft maturation: IHC (Rod-POS development) 2 Host-graft synapse formation: IHC [presynaptic (CtBP2) and post-synaptic (CaV1.1) proteins] 3 Light signal transmission to host RGCs: Multi-electrode array recording and two-photon Ca^{2+} imaging 4 Improvement in behavioral tests of vision: Shuttle Avoidance System Test	Matsuyama et al. [40]
• Crx-GFP hESC (H9)-derived RO (DD28-30, 50–59, and 169–186) + Human ESC (H9)-derived RPE	• RCS nude rats: P46-66	1 Graft maturation: IHC (Rod-POS development and Best1-positive RPE) * No IHC on synaptic proteins 3 Light signal transmission to cortex: Superior Colliculus Electrophysiology 4 Improvement in behavioral tests of vision: Optokinetic Response Testing	Thomas et al. [29]
• Crx:Venus hESC (KhES-1)-derived RO (DD60) • Crx:Venus ISL1−/− hESC (KhES-1)-derived ROs (DD60)	• SD-Foxn1 Tg (S334ter) 3Lav nude rats: 16–25 weeks old	1 Graft maturation: IHC (Rod/Cone-POS development, phototransduction proteins, and interphotoreceptor matrix) 2 Host-graft synapse formation: IHC [synaptic molecules (CtBP2, PSD95, LRIT3, Pikachurin, CaV1.1, and mGluR6)] 3 Light signal transmission to host RGCs: Multi-electrode array recording	Yamasaki et al. [56]

Numbers (1–4) in the "Findings" column indicate the primary levels of proof-of-concept demonstrated in each study: (1) graft maturation (POS) development; (2) host–graft synapse formation; (3) light signal transmission to host RGCs; and (4) improvement in behavioral tests of vision.

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; DD, differentiation day; EM, electron microscope; ESC, embryonic stem cell; GFP, Green Fluorescent Protein; IHC, immunohistochemistry; iPSC, induced pluripotent stem cell; POS, photoreceptor outer segment; PRC, photoreceptor cell; RCS, Royal College of Surgeons; RGC, retinal ganglion cell; RD, retinal degeneration; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; RO, retinal organoid.

cell lines for PRC enrichment [14,15], such reporter cell lines are not permissible for clinical application. Accordingly, recent efforts have focused on label-free enrichment methods, aiming to isolate relatively immature PRC precursors with translational potential, as discussed later in this review.

2.2. *Retinal sheet transplantation modalities (Table 3)*

Retinal sheet transplantation exhibits several advantages (Table 1). First, graft survival and long-term engraftment have been demonstrated in preclinical studies [5]. Our group obtained proof-of-concept data using hESC/hiPSC-derived RO sheets in end-stage retinal degeneration animal models, documenting graft PRC maturation, host–graft synapse formation, and transmission of light-evoked signals to host retinal ganglion cells (RGCs) over long-term follow-up [4,5,33]. Second, RO sheets reportedly not only exhibit low immunogenicity but also possess immunosuppressive properties, partly via TGF-β–mediated induction of regulatory T cells [34]. In retinal degeneration NHP models, both MHC-matched and mismatched sheets have been transplanted without systemic immunosuppression, showing no clinical signs of rejection and histological evidence of PRC maturation [35]; nonetheless, mild immune responses—including lymphocyte accumulation in the choroid adjacent to the graft and positive results on the lymphocyte graft immune reaction assay [36], which evaluates proliferation of recipient peripheral blood mononuclear cells against the graft—suggest that some degree of immunosuppression may still be advisable in clinical settings. Third, the presence of supporting cells in the graft, such as horizontal cells and Müller glial cells [37,38], may not only promote better alignment of graft PRCs, thereby facilitating POS development, also support host-graft synaptic connections [39].

In contrast, several disadvantages merit consideration (Table 1). First, regardless of whether a transvitreal or transscleral approach is used, delivering a 1.0–1.5 mm^2 sheet into the subretinal space makes the procedure more complex than cell suspension injection. Second, although sheet grafts usually maintain PRC alignment, residual inner retinal cells within the graft—pre-formed synapses between graft-PRCs and graft-BCs—may disturb opportunities for host–graft synaptic connections [40]. Finally, although identical cell doses cannot be matched across modalities and strict head-to-head comparisons are difficult, rosette formation can occur with both modalities, but tends to be larger in sheet modalities.

Rosette structures are generally considered functionally suboptimal, because POSs in these structures do not directly contact the RPE, thereby limiting RPE-mediated phagocytosis of POSs and visual-cycle renewal. Nevertheless, long-term follow-up in NHP models has shown enhanced GFAP immunoreactivity at the RPE-facing side of rosettes, suggesting that some graft PRCs may ultimately reorganize into semispherical open structures with POSs oriented toward the RPE, which better approximates physiological architecture [5]. Strategies under investigation to promote host–graft integration include gene-editing approaches, as discussed later.

3. Clinical translation: first-in-human trial for RP

Building on safety and efficacy in preclinical animal studies, Hirami et al. performed allogeneic RO sheet transplantation in two subjects with advanced RP (jRCTa050200027), using a clinical-grade hiPSC-QHJI01s04 line provided by the Kyoto University Center for iPS Cell Research and Application (Fig. 1A) [8]. The iPSC-derived ROs were generated by a modified SFEBq protocol with SB431542 and smoothened agonist (SAG) preconditioning, BMP4 treatment, and induction-reversal culture, as previously described [41–43]. ROs were dissected at 70–90 days of differentiation to prepare approximately 0.5 × 1 mm retinal sheets, of which three were transplanted per eye to regions with no photosensitivity on visual field testing but with a residual RPE layer identified by optical coherence tomography (OCT) and fundus

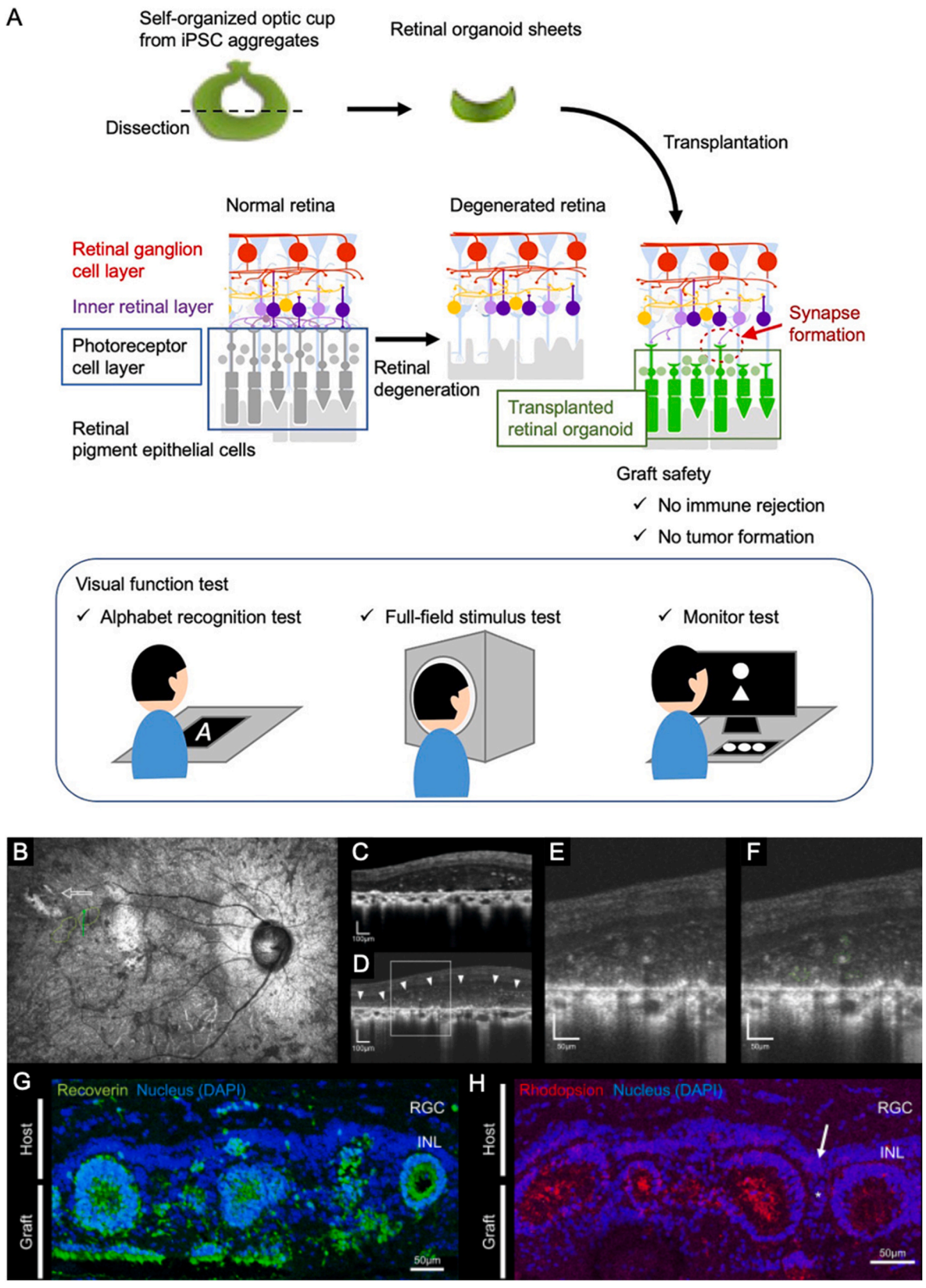

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Fig. 1. First-in-Human Trial of Human iPSC-Derived Retinal Organoid (RO) Sheet Transplantation. (A) Overview of the first-in-human clinical trial. Three RO sheets on differentiation day 70–90 were transplanted into subretinal space in one eye of two patients. In addition to routine visual function tests, three types of tests for low vision—alphabet recognition test, full-field stimulus test, and monitor test— were performed before transplantation and at 24, 36, 52, and 104 weeks after transplantation. (B) Scanning laser ophthalmoscopy image on the transplanted eye. White arrow indicates the incision for transplantation of the RO sheet, and the dotted lines indicate the transplantation area. The green line indicates the optical coherence tomography (OCT) scan path. (C) OCT image of the transplantation site. (D) Adaptive optics OCT (AO-OCT) images of the same site. A high-resolution view detailing the outer plexiform layer (OPL) like line (arrowheads) and possible arrangement of the photoreceptors cells (PRCs) were provided. (E and F) Magnified AO-OCT image showing a detailed view of the rosette-like arrangement of the PRCs in the graft (green: PRCs; yellow: outer segments). (G and H) Immunostaining images of human iPSC-derived retinas in a monkey model of retinitis pigmentosa with laser ablation of PRCs. A rosette-like, RCVRN (green, G)-positive graft PRCs are observed, with RHO (red, H)-positive outer segment structures on its inner side. The graft inner nuclear layer (INL, asterisk) possibly merges with the host INL (white arrow). Nuclear staining shows the presence of OPL-like spacing between the graft photoreceptors and host/graft INL. Scale bars: 100 μm (C and D) and 50 μm (E–H). (A) Adapted from Ref. [8] (with permission). (B-H) Adapted from Ref. [44].

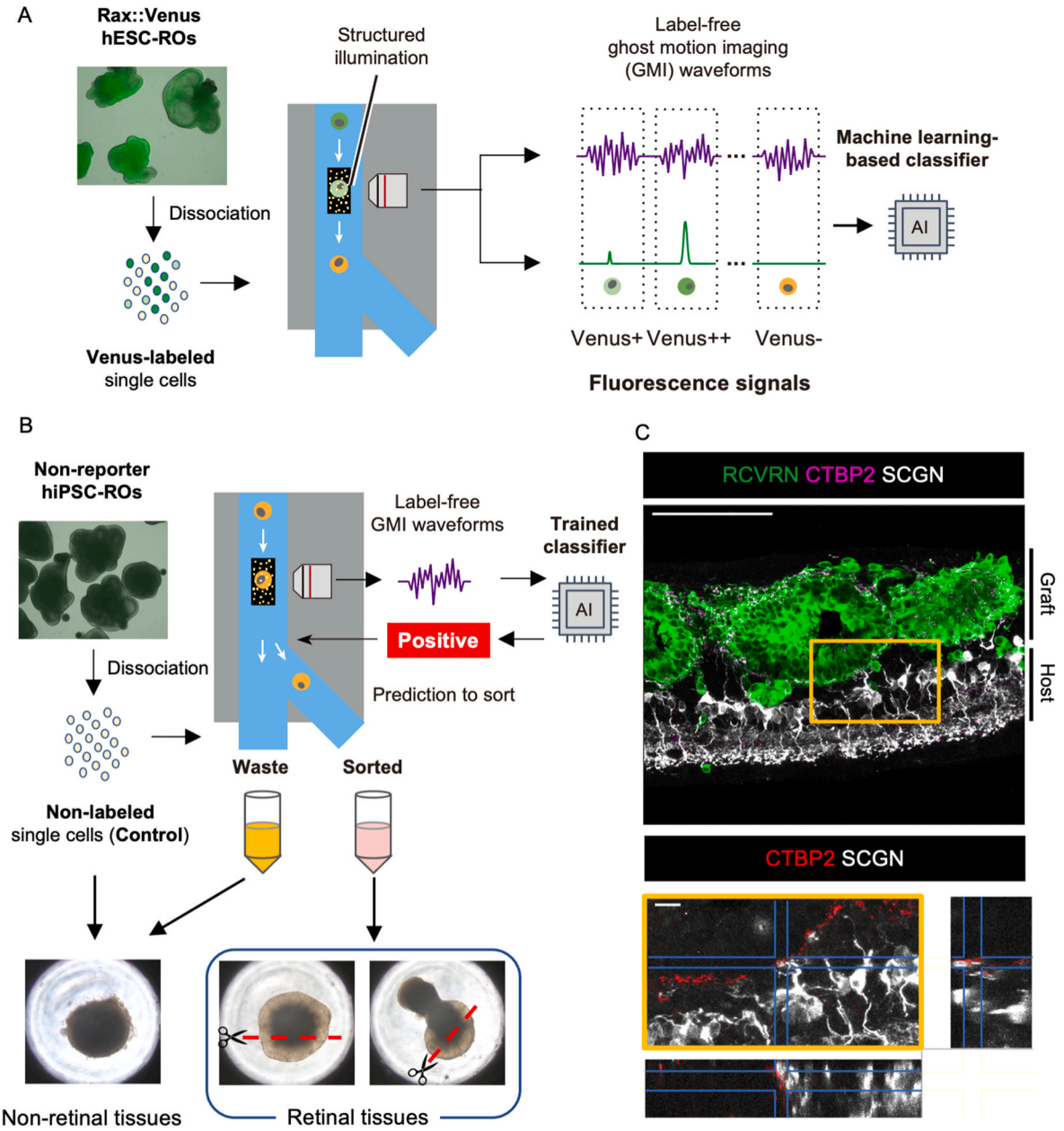

Fig. 2. Label-free ghost cytometry (LF-GC) based enrichment of human pluripotent stem cell-derived retinal progenitor cells (A) Scheme for obtaining the label-free ghost motion imaging (LF-GMI) waveforms. The LF-GMI waveforms and Venus fluorescence signals (ground truth labels) of Rax:Venus cells were acquired using a GC setup. (B) Scheme of LF-GC-based sorting for retinal progenitor cell enrichment and spheroid formation experiments. In sorting, each cell was classified as positive or negative in real time based on the trained classifier using FSC-H, BSC-H, and LF-GMI waveforms. Subsequently, the positive cells were sorted and collected as Sorted. Original and negative (non-sorted) samples were defined as Control and Waste, respectively. (C) Immunostaining images of ribbon synapse at the graft photoreceptor cell (PRC) axon terminals. Potential contacts were found between the dendritic tips of extending SCGN-positive (white) host cone bipolar cells and RCVRN-positive (green) graft PRCs. Magnified views of the orange boxes are shown below, showing ribeye protein (CTBP2, red or magenta) expression by graft PRCs at the host-graft interface. Scale bars: 100 μm (C, top) and 10 μm (C, bottom). Adapted from Ref. [54].

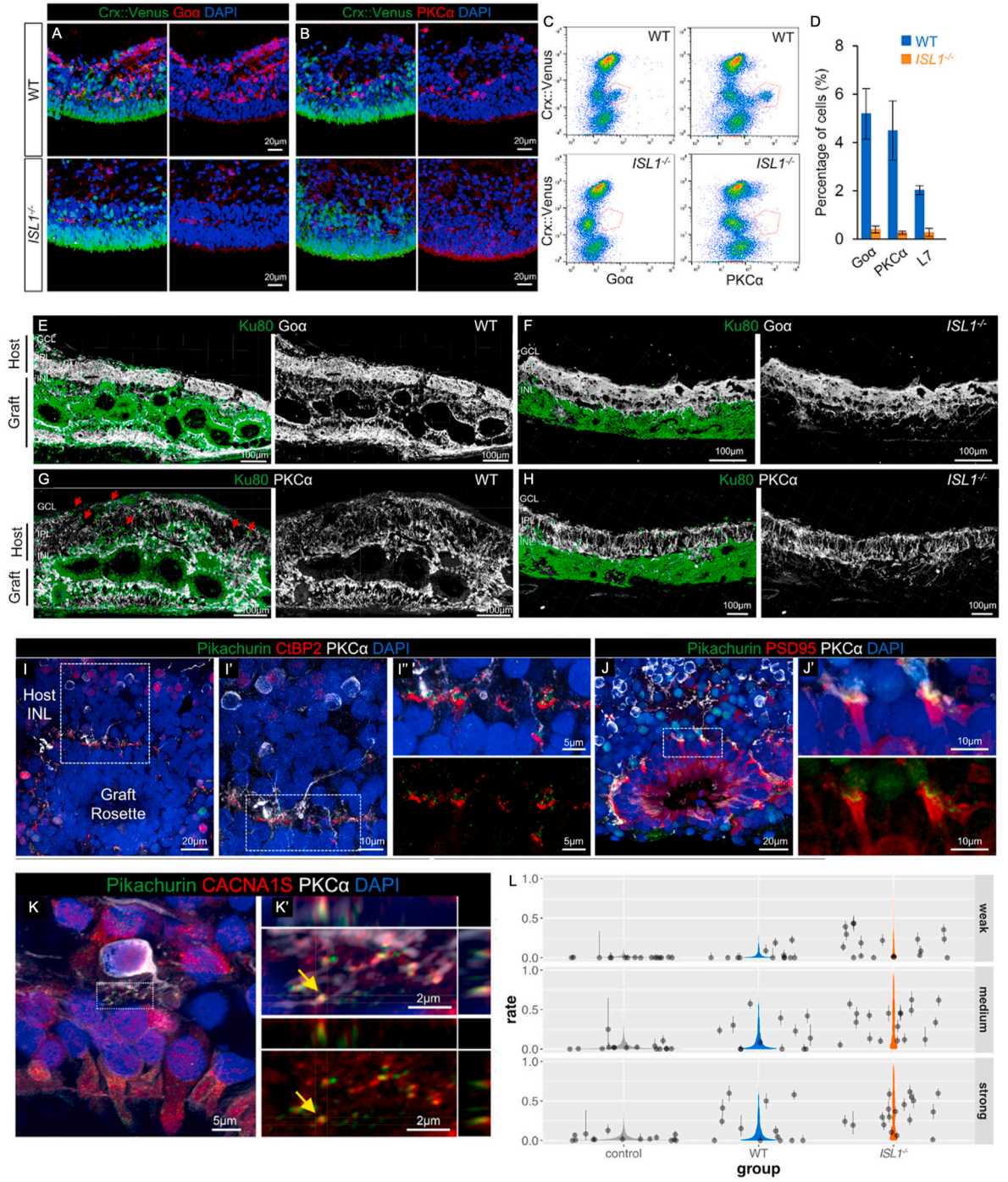

Fig. 3. Characteristics of *ISL1*$^{-/-}$ hESC-derived retinal organoids (ROs) and their improved structural and functional integration after RO sheet transplantation into a retinal degeneration rat model. (A–D) Representative immunostaining images (A and B) and flow cytometry plot (C) for wild-type (WT) and *ISL1*$^{-/-}$ hESC-derived RO on around differentiation day 240. The populations of PKCα-positive rod bipolar cells (BCs) and L7-and GOα-positive ON BCs were reduced in *ISL1*$^{-/-}$ hESC-derived ROs (D). (E–H) Immunostaining images of the graft cells and ON/rod BCs. The graft cells are labeled with the primate-specific nuclear marker Ku80 (green). In *ISL1*$^{-/-}$ hESC-derived RO grafts (F and H), GOα-positive ON BCs (white; panels E–F) and PKCα-positive rod BCs (white; panels G–H) were reduced compared with WT grafts (E and G). (I–K) Immunostaining images showing presynaptic and postsynaptic proteins. Presynaptic proteins Pikachurin (green) and CtBP2 (red, I), as well as PSD95 (red, J), were localized at the dendritic tips of PKCα-positive host rod BCs. Postsynaptic Cacna1s (red, K) was observed in close apposition to Pikachurin, indicating potential synaptic coupling. (L) Summary of retinal ganglion cell (RGC) response probability with light stimulation in multiple electrode array. Host RGCs with the *ISL1*$^{-/-}$ graft exhibited light-evoked responses in a greater number of retinas across all light intensities, including at lower light levels, compared with those with WT grafts and non-transplanted control retinas. Scale bars: 100 μm (E–H) and 20 μm (A, B, I, and J), 10 μm (I′ and J′), 5 μm (I″ and K), and 2 μm (K′). Adapted from Ref. [56].

autofluorescence images. After pars plana vitrectomy, a glutathione-containing irrigating solution was injected into the subretinal space via a 38-gauge cannula to create a careful artificial retinal detachment; a 1-mm retinal incision was then made and RO sheets were delivered through a 24-gauge plastic cannula. Intravitreal and sub-tenon administration of 20 mg of triamcinolone acetonide was performed at the end of the surgery, and 3 mg/kg/day of cyclosporine was administered orally for 6 months after transplantation to suppress the immune response.

Two years after transplantation, the grafts survived without serious adverse events, including signs of immune rejection. Although no significant change in visual function was observed at 2 years after transplantation relative to baseline, one subject showed mild improvements across three independent visual function tests at 1 year after transplantation, suggesting a possible therapeutic benefit. While histological testing was not feasible, adaptive optics-OCT examination revealed rosette-like structures with outer-segment-like features within the graft, forming an outer plexiform layer-like line adjacent to the host inner nuclear layer (Fig. 1B–H). [44]. These findings are similar to those reported in NHP studies, suggesting the possibility of post-transplant PRC maturation and integration. Taken together, this first-in-human study supports safety and graft survival (Fig. 1A), with current challenges centered on (1) graft production efficiency—because the efficiency of producing ROs with sufficiently large retinal areas for graft excision varies among hiPSC lines, and ROs with small retinal portions cannot be used—and (2) host–graft integration, as graft PRCs can mature but synaptic connections between host and graft are formed only to some extent. Future directions include robust graft manufacturing and evaluation of improved grafts in longer-term trials to assess clinical benefit.

4. Emerging bioengineering solutions

4.1. Label-free enrichment

In cell suspension transplantation, as noted above, purification of PRCs using microfluidic cell sorting devices represent a critical step. Because relatively mature PRCs express specific surface antigens [45,46], several studies have attempted to enrich PRCs based on markers such as CD73 [47,48] or combinations of surface antigens [46,49]. However, given the labor and financial costs as well as the potential cytotoxicity of molecular staining on the final product, such approaches are generally avoided in clinical-grade manufacturing. Recent studies have attempted label-free enrichment of PRC precursors by exploiting distinct biophysical properties. Stone et al. demonstrated the enrichment of human PRC precursors from mixed suspensions with RPE cells based on cell stiffness and viscosity [50], while Herbig et al. applied bright-field image–based classification to NRL::GFP-mouse PRC precursors, achieving an enrichment factor of 2.7, corresponding to an increase in the NRL::GFP-positive fraction from 53.2 % to 69.5 % [51,52]. These efforts illustrate the potential of label-free strategies, but achieving the practical application of these technologies in terms of quality control and clinical-scale throughput remains challenging.

For retinal sheet transplantation, one strategy to achieve robust graft production efficiency is the enrichment of retinal progenitor cells (RPCs) from early-stage ROs, thereby enabling the collection of RPCs from all ROs regardless of their initial RPC content to ultimately generate stable retinal tissues. The main issue of this strategy is that no specific surface antigens have been reported for early-stage RPCs [46,49]. To detect early-stage RPCs, our group applied for ghost cytometry (GC) technology, a recently developed high-content flow cytometric approach that enables fast and accurate analysis of cells based on their high-resolution structural information down to the subcellular levels [53,54]. We trained the classifier of the GC system using a human ESC-derived Rax::Venus RPC reporter line (Fig. 2A), and successfully enriched RPCs lacking specific surface antigens from unlabeled human ESC/iPSC lines, enabling the reproducible formation of retinal tissues suitable for transplantation (Fig. 2B). When transplanted into rat models of retinal degeneration, these tissues exhibited structural features suggestive of functional integration (Fig. 2C). With some cell lines, label-free GC-based enrichment achieved the production of over 90 % transplantable spheroids, which could be readily processed for graft excision. This approach enables the stable and robust production of retinal grafts, allowing up to a tenfold increase in graft production efficiency.

4.2. Gene-edited cell line

Another challenge is that only a fraction of graft PRCs form synaptic connections with the host retina. One possible explanation is that graft PRCs have already established synaptic connections with graft-derived BCs, making it difficult to generate new synaptic connections with host BCs. To address this issue, our group adopted a strategy to reduce the number of graft BCs by using genetically engineered ESCs/iPSCs lacking *ISL1*, a gene essential for BC development and maturation [40,55,56]. Yamasaki et al. demonstrated that *ISL1*$^{-/-}$ human ESC-derived ROs showed reduced numbers of secondary retinal neurons while maintaining an intact PRC cell layer structure (Fig. 3A–D). In addition, they transplanted *ISL1*$^{-/-}$ human ESC-derived RO sheets into rats with advanced retinal degeneration and found that the numbers of ON- and rod-BCs within the graft were decreased compared with wild-type controls (Fig. 3E–H), while host BCs established synaptic connections with graft PRCs (Fig. 3I–K). Expression of L/M − and S-opsins in the outer segments was also observed, and both light-evoked RGC responses and sensitivities were improved after transplantation (Fig. 3L). In summary, *ISL1*$^{-/-}$ human ESC-derived RO sheets were suggested to achieve more efficient host–graft integration compared with wild-type ROs. A clinical trial using genetically engineered *ISL1*$^{-/-}$ human iPSC-derived RO sheets is currently being prepared, with the expectation of greater improvements in visual function after transplantation.

5. Expanding indications into macular diseases

While rod-PRC replacement has been the primary focus in RP, cone-PRC preservation and restoration are crucial for central vision due to their predominance in the macula [6,57]. A recent study demonstrated that subretinal transplantation of human iPSC-derived cone-PRC suspensions resulted in successful graft integration with correct PRC polarity within the host ONL, extension of host Müller glial cells throughout the graft, and cone-mediated electrophysiological responses in a cone-PRC degeneration mouse model [7]. Although material transfer was ruled out in this report, given the importance of the macula in primates, the use of NHP models that recapitulate pathological conditions in the macular region would be ideal. In our group, preclinical experiments using genome-edited human ESC-derived RO sheets lacking ON-BCs (*ISL1*$^{-/-}$) were performed in NHP models of macular hole [58] and laser-induced macular degeneration [59].

Macular hole (MH) is a retinal break involving the fovea that causes visual impairment. Although advances in vitreoretinal surgical techniques have achieved closure rates exceeding 90 %, refractory cases still exist. In such difficult cases, autologous retinal transplantation has been conducted with good anatomical success [60], however postoperative visual recovery is generally limited. We transplanted *ISL1*$^{-/-}$ human ESC-derived retinal sheet into the MH space of a NHP model with a presumed idiopathic MH (Fig. 4A) [58]. After transplantation, MH was successfully closed by continuous filling of the MH space with the RO sheet (Fig. 4B and C), resulting in improved visual function in fixation and electrophysiological tests (Fig. 4D). Histological analysis confirmed the presence of rod and cone PRCs in the graft, but not with synaptic connections between the host and graft, possibly due to mild immune rejection that may have caused secondary gliosis caused by the impaired differentiation of some retinal cells in the graft (Fig. 4E, F, and 4G). In laser-induced macular degeneration models, host rod- and cone-BCs extended dendrites toward grafted PRCs to form synapses (Fig. 4H–K),

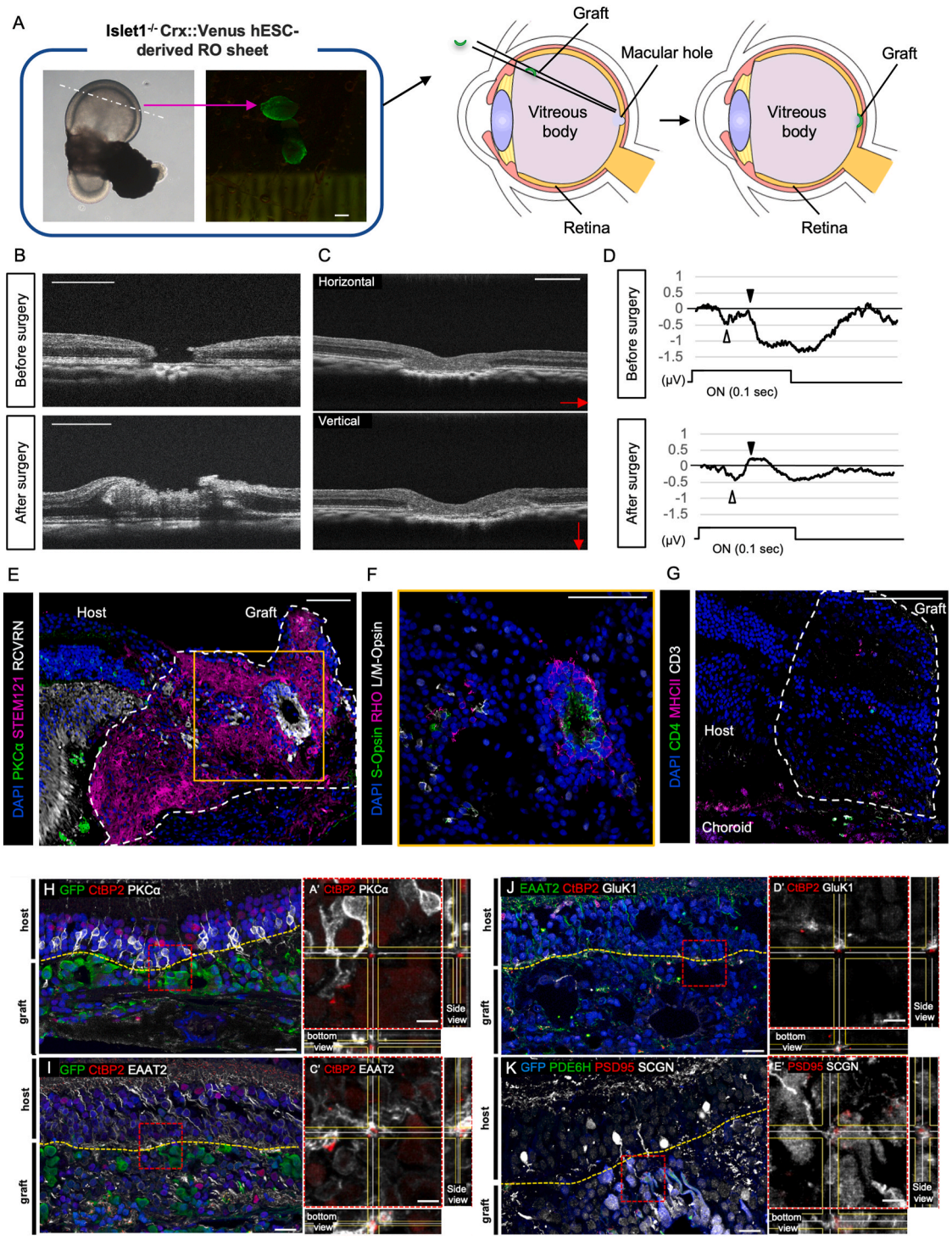

Fig. 4. Transplantation of *ISL1*$^{-/-}$ hESC-derived retinal organoid (RO) sheets into non-human primate (NHP) models of macular hole (MH, 4A-4G) and laser-induced macular degeneration (4H–4K) (A) Overview of transplantation of *ISL1*$^{-/-}$ hESC-derived RO sheet into the NHP model with MH. Crx:Venus-positive and continuous retinal epithelium parts of ROs were cut into sheets (green), and one of them was transplanted into MH space. (B) Intraoperative optical coherence tomography (OCT) image of the foveal area before (top) and after (bottom) retinal transplantation. (C) OCT images at 6 months after transplantation. Retinal graft filled in the MH space. (D) Focal macular electroretinograms recorded with a 5°-circle stimulus spot on the transplanted eye. The amplitude of the a-wave (white arrow) was small and showed no remarkable differences before and after transplantation (0.47 vs. 0.40 mV, respectively). In contrast, The b-wave amplitude (black arrow) increased from 0.43 mV before surgery to 0.70 mV at 6 months after surgery. (E–G) Immunostaining images of host-graft interface in the MH eye. STEM121-positive human graft tissue (magenta, E) occupied the host MH space, where rosette-like structures of RCVRN-positive photoreceptors (PRs, white, E) were observed. Grafted PRs expressed RHO (magenta, F), OPN1LW/OPN1MW (white, F), and OPN1SW (green, F). CD4-positive T cells (green, G) were present within the graft, indicating that mild rejection responses had occurred. (H–K) Immunostaining images of synaptic connections between host bipolar cells (BCs) and grafted PRs. The presynaptic marker CtBP2 was localized at the margins of Crx:Venus PRs and at the dendritic tips of PKCα-positive rod BCs (H) and EAAT2-positive cone BCs (I). Co-localization of CtBP2 (presynaptic protein) and GluK1 (postsynaptic protein) was observed at the dendritic tips of EAAT2-positive cone BCs (J). The presynaptic marker PSD95 was detected at the margins of GFP- and PDE6H-positive grafted cone PRs and at the dendritic tips of SCGN-positive cone BCs (K). Scale bars: 500 μm (A, C), 200 μm (B), 100 μm (E–G) 15 μm (H–K). 4 μm (H′-K′). (A–G) Adapted from Ref. [58]. (H–K) Adapted from Ref. [59].

thereby rebuilding both ON- and OFF-pathway connectivity and providing the first demonstration of host–graft synaptic integration in the NHP macula [59]. These findings suggest that genome-edited pluripotent stem cell-derived RO sheet transplantation could serve as a practical option for refractory MH and macular degeneration treatment.

6. Conclusions and future directions

This review has outlined the current status of cell-based regenerative therapy for retinal diseases, highlighting both the challenges revealed by the first-in-human trial for RP patients using iPSC-derived ROs and recent bioengineering advances aimed at overcoming them. The field has progressed beyond preclinical proof-of-concept studies in animal models and is now entering a new stage of clinical exploration. Other important issues not discussed in detail here include the difficulty of evaluating efficacy in patients with ultra-low visual function, and the substantial costs associated with safety testing of graft tissue and clinical-grade cell/tissue manufacturing. Addressing these scientific and practical challenges will be essential before retinal cell-based regenerative therapy can be reliably implemented in clinical practice.

Author contributions

Conceptualization: Y·I., T.M., and M.M.; Writing-Original Draft: Y·I.; Writing-Review & Editing: Y·I., T.M., A.M., K.E., and M.M.; Supervision: M.F., K·N., and M.M.; All authors reviewed and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the writing of this review.

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