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Curved-Tip Disposable Injector (OUReP Injector) to Insert Photoelectric Dye-Coupled Polyethylene Film (OUReP) as Retinal Prosthesis into Subretinal Space of Rabbit Eyes

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Abstract

The photoelectric dye-coupled thin polyethylene film functions as a novel type of retinal prosthesis in subretinal space of the eye. We previously reported a novel disposable injector to insert the thin film into subretinal space of the rabbit eye by vitreous surgery. The injection system composed of two separate parts, injector and loader. A circular film in 5 mm to 10 mm diameter was pulled into a transparent tube of the loader with a commercial 25-gauge forceps. The loader tube was joined with a sleeve to tube tip of the injector. The film in the loader was pushed with a plunger for the loader into the injector tube tip. The loader with the sleeve was removed from the injector tip, and the tube tip with the film was filled with solution. This study reported a small-bore curved-tip disposable injector with outer diameter of 1.6 mm. A curved-tip polypropylene tube was formed by the process of heating and cooling of the tube inserted with a curved guide wire. The plunger for the curved-tip tube was made of a polyphenylsulfone tip connected with a press-fitting inner polypropylene tube to a nylon rod. Bleb retinal detachment in 4 surgically aphakic eyes of rabbits were induced by infusing solution into subretinal space with a 38-gauge polyimide tip, and a retinal tear was made at the edge of retinal detachment with 25-gauge diathermy. The injector tip with the rolled film in 6 mm diameter was inserted from 2 mm wide scleral incision into vitreous and then into subretinal space. The rolled films were released into subretinal space with the tip end inserted into the retinal tear, and the released films were confirmed to stay under the retina with no additional aid. Dissection one month after surgeries confirmed successful implantation of 4 films into subretinal space of each rabbit eye. The curved-tip injector could release the rolled film into the subretinal space without additional effort, compared with the straight-tip injector, and would help surgeons implant photoelectric dye-coupled thin film retinal prosthesis easily at vitreous surgery.

Keywords: Dye-coupled thin film retinal prosthesis; Curved-tip injector; Photoelectric dye; Rabbit; 25G vitrectomy

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Introduction

A preloaded disposable injector for intraocular lens is currently used as a standard tool at cataract surgery to insert foldable acrylic intraocular lens into capsular bag of the lens in human patients. Small incision about 2 mm allows the insertion of standard intraocular lens with the diameter of 6 mm. Rabbit eyes were, for instance, used to test the deformation of corneal incision from which different kinds of intraocular lens injectors, available at the market, were inserted [1]. We have been developing a photoelectric dye-based retinal prosthesis to replace the function of lost photoreceptor cells and to stimulate the remaining retinal ganglion cells which send their axons as the optic nerve to the brain [2-6]. The retinal prosthesis is made of photoelectric dye-coupled polyethylene thin film which works as both the light-receiver and the electric potential generator to stimulate nearby neurons in response to light [7-12]. The thin polyethylene film is soft and foldable, and has to be inserted in the subretinal space of the eye [13-15]. In our previous study, we developed

a disposable injector for dye-coupled thin film retinal prosthesis and tested the insertion of the thin film in rabbit eyes [16]. In this study, we designed a small-bore curved-tip disposable injector to insert the thin film easily into the subretinal space of rabbit eyes.

Materials and Methods

Preparation of dye coupled polyethylene film

Thin films were made from polyethylene powder and exposed to fuming nitric acid to introduce carboxyl moieties on the film surface. Photoelectric dye molecules, 2-[2-[4-(dibutylamino)phenyl]ethenyl]-3-carboxymethylbenzothiazolium bromide (NK-5962, Hayashibara, Inc., Okayama, Japan), were coupled to carboxyl moieties of the polyethylene film surface *via* ethylenediamine, as described previously [7,17-21]. The dye-coupled films were manufactured in quality management system at a clean-room facility in the Okayama University Incubator.

Animals

Normal male white rabbits (Kbl: JW, specific pathogen free, Kitayama Labes Co., Ina City, Japan) at the age of 14 to 15 weeks were used in this study. Table 1 shows the number of rabbits used in the series of studies which were conducted at 4 different sessions. Only the right eyes were operated-on, and the left eyes served as controls. One month after dye-coupled film implantation, animals were sacrificed by bleeding with overdose of intravenous pentobarbital sodium (0.7 to 0.9 mL/kg body weight, water solution 64.8 mg/mL, Tokyo Chemical Industry Co., Tokyo, Japan), and the eyes were enucleated. The eyes were then fixed with phosphate-buffered 2.5% formaldehyde and 3% glutaraldehyde, dissected for photography, and further processed for pathological sections with hematoxylin-eosin stain. This study was approved by the Animal Care and Use Committee in Okayama University and also by the Committee at Shin Nippon Biomedical Laboratories, Inc., based on the Animal Welfare and Management Act in Japan (IACUC736-009, IACUC736-010, IACUC736-011, and IACUC736-012).

Surgical procedures

Rabbits were anesthetized with a 4:1 mixture (1.2 mL/kg body weight) of intramuscular ketamine (50 mg/mL, Ketamine 5%, Supriya Life Science, Mumbai, India) and xylasine (20 mg/mL, Celactal 2%, Bayer Animal Health, Tokyo, Japan), together with intradermal buprenorphine (0.05 mg/ kg body weight, Lepetan 0.2 mg, Otsuka Pharmaceutical, Tokyo, Japan). Mydriasis in both eyes was induced by 0.5% tropicamide and 0.5% phenylephrine eye drops (Mydrin-P, Santen Pharmaceutical, Osaka, Japan) on the day of surgery. After disinfection with 10% povidone iodine (Negmin Solution, Pfizer Japan, Tokyo) on the haired skin around the eye and then with 40 time saline diluted povidone iodine on the ocular surface, the rabbit's head was positioned on the left side down for surgery at the right eye, and covered with a surgical drape. Topical anesthesia was further obtained with 4% lidocaine (Xylocaine Ophthalmic Solution, Astra Zeneka, and London, UK). The surgery was done under a surgical microscope (OPMI VISU 150, Carl Zeiss Meditec, Tokyo, Japan) with a surgical machine (Constellation Vision System, Alcon Laboratories, Inc., Fort Worth, TX, USA) [16]. Anterior capsulectomy (Figure 1A) was done with a 25-gauge vitreous cutter under irrigation with a 25-gauge infusion cannula through two side ports which were made at the corneal limbus with a 20-gauge knife (V-Lance Knife, Alcon) [22]. Phacoemulsification and aspiration of the lens in the capsular bag (Figure 1B) was done through a 2.4 mm wide corneal incision

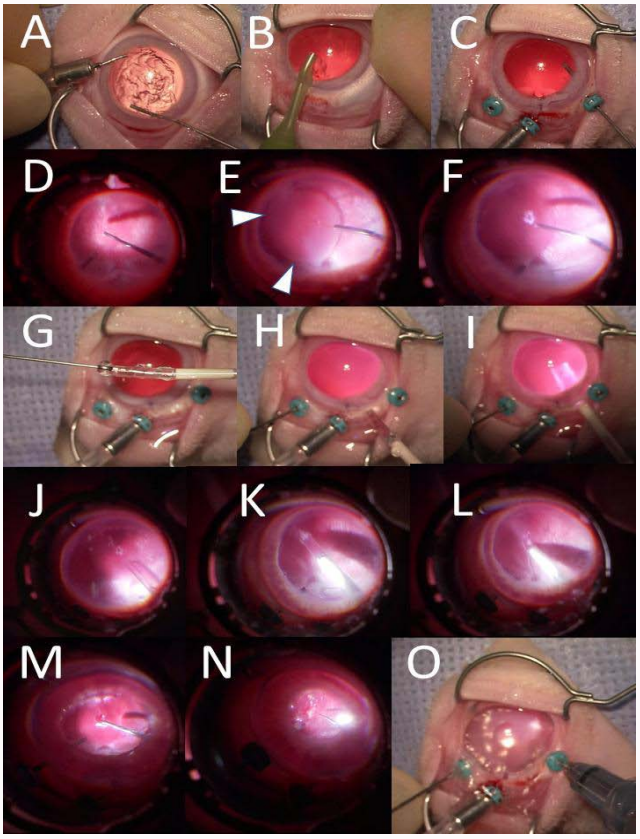

Figure 1: Surgical procedures to implant the photoelectric dye-coupled thin polyethylene film (OUReP) with a curved-tip disposable injector (OUReP Injector). A) Lens anterior capsule is cut with 25G vitreous cutters under irrigation with 25G infusion cannula in the anterior chamber. B) Lens nucleus and cortex is aspirated with phaco-emulsification tip from the corneal incision. C) After conjunctival incision, three 25G trocars are inserted through the sclera into the vitreous at 2 mm from the corneal limbus: A middle trocar is connected with infusion cannula, and the other two trocars are used for vitreous cutter and light guide. Posterior capsule is cut with vitreous cutter. D) Vitreous gel is cut thoroughly. E) Bleb retinal detachment (arrowheads) is made by 38G tip infusion of intraocular irrigating solution. F) A retinal tear (white spot) is made by retinal coagulation with 25G bipolar diathermy. G) After scleral incision is made, OUReP injector tip with 6 mm diameter circular film is filled again with irrigating solution with a 27 gauge blunt-end needle. H) and I) Injector is inserted from scleral incision into vitreous cavity. J) and K) Injector tip is inserted into sub-retinal space through a retinal tear. L) Plunger of the injector is pushed to release the film into sub-retinal space. M) Fluid-air exchange in vitreous cavity is done and sub-retinal fluid is aspirated with 25G vitreous cutter in aspiration mode. N) After retinal reattachment with air in vitreous cavity, laser coagulation is applied around the retinal tear. O) Silicone oil is injected in vitreous cavity with 25G tip.

made on the superior side with a disposable knife (Safety Knife, Kai Medical, Seki, Japan). The corneal incision was sutured with 8-0 Vicryl (polyglactin 910) suture (Ethicon, Johnson & Johnson, New Brunswick, NJ, USA). After conjunctival incision, three 25-gauge trocars were inserted perpendicularly into the vitreous through the sclera 2 mm from the limbus on the superior to temporal side within 120 degrees of meridian (Figure 1C). The presence of a large vascularized nictitating membrane on nasal side of the conjunctiva limited the surgical area used for placing trocars [14,16]. Posterior capsulectomy was done with a vitreous cutter under irrigation with a 25-gauge cannula placed at the middle trocar on the superior side (Figure 1C). The wide-field fundus was viewed with a +128-diopter front lens by Resight 500 fundus viewing system (Carl Zeiss Meditec). After core vitrectomy (Figure 1D), bleb retinal detachment was

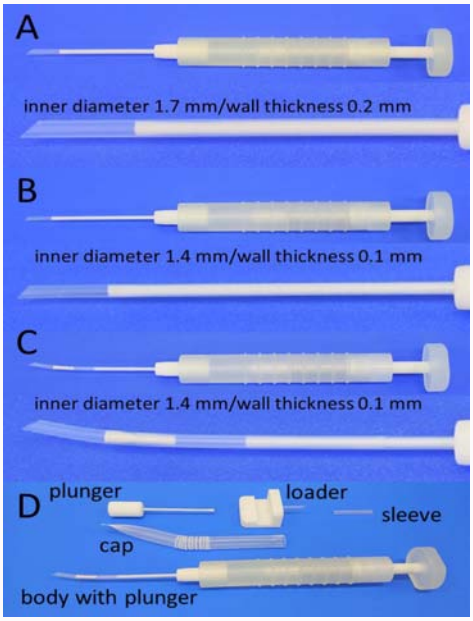

Figure 2: Disposable thin film injector (OUReP Injector) in different gauges. A) Straight-tip injector with large gauge (inner diameter 1.7 mm with wall thickness 0.2 mm). B) Straight-tip injector with small gauge (inner diameter 1.4 mm with wall thickness 0.1 mm). C) Curved-tip injector with small gauge (inner diameter 1.4 mm with wall thickness 0.1 mm). D) Entire set of loader and curved-tip injector.

made by infusing irrigation solution (BSS-Plus Intraocular Irrigating Solution, Alcon) into the subretinal space with a 38-gauge polyimide tip (Poly Tip Cannula 25G/38G, Med One Surgical, Inc., Sarasota, FL, USA) attached to a 10-mL syringe for the Viscous Fluid Control (VFC) system at the setting of low intraocular pressure (Figure 1E). A retinotomy was made by 25-gauge diathermy (Grieshaber Diathermy Probe DSP 25Ga, Alcon) at the edge of retinal detachment (Figure 1F). A 2 mm to 3 mm wide scleral incision was placed with a microsurgery knife (Straight/Stab 22.5°, Kai Medical) 2 mm posteriorly in parallel with the corneal limbus, and wound hemostasis was done with a wet-field hemostatic eraser bipolar instrument (Beaver-Visitec International, Inc., Waltham, MA, USA). An injector tip with a dye-coupled film was filled again with solution (Figure 1G) and inserted through the scleral incision (Figure 1H) into the vitreous (Figure 1I) and then under the detached retina *via* a retinotomy (Figure 1J and 1K). The film was released into the subretinal space (Figure 1L) by pushing the plunger with index finger while the body of the injector was held with thumb and other fingers. The plunger was pushed back automatically by a coil spring inside the injector [16]. The scleral incision was sutured with 8-0 Vicryl (polyglactin 910) suture (Ethicon). The subretinal fluid was aspirated with a vitreous cutter, and then fluid in vitreous cavity was exchanged with air to reattach the retina (Figure 1M). Laser photocoagulation was applied around the retinal tear caused by retinotomy (Figure 1N), and silicone oil (polydimethylsiloxane, Silikon 1000, Alcon) was injected into vitreous cavity by the VFC syringe (Figure 1O). Trocars were removed, and the conjunctiva was sutured with 8-0 Vicryl suture [16]. Sham surgery had all procedures except for injecting the film in the subretinal space by the injector.

Results

Design of injector

The disposable entire system was composed of two separate parts,

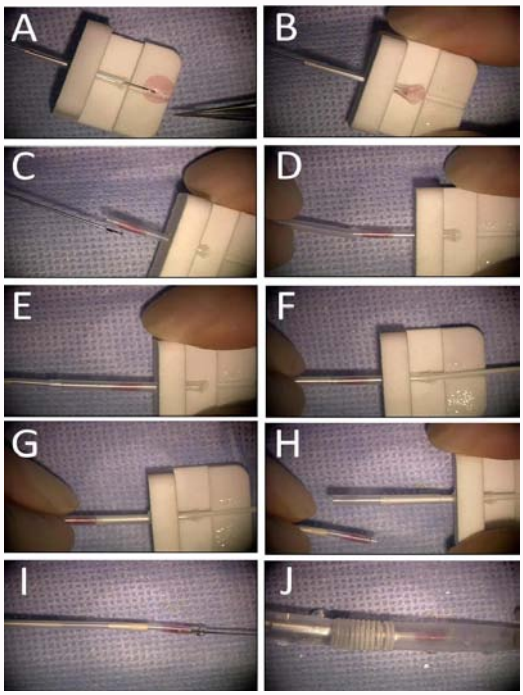

Figure 3: Procedures to put a piece of thin film into tube tip of small-bore curved-tip injector. A) Circular dye-coupled film in 6 mm diameter is placed on the loader plate. B) and C) The film is pulled into a transparent tube of the loader with a commercial 25-gauge forceps (Grieshaber Revolution DSP 25Ga ILM Forceps, Alcon), which is inserted into the tube from the opposite side. D) and E) The loader tube is joined with a sleeve to the tube tip of the injector. F) and G) The film in the loader is pushed with a plunger for the loader into the tip of the injector tube. H) The loader with the sleeve is removed from the injector tube tip. I) The tube tip with the film is filled with intraocular irrigating solution, using 27-gauge blunt-end needle attached to a 2.5 ml disposable syringe. J) The tube tip with the film is put into solution-filled cap.

an injector with a plunger and a loader tube fixated on the plate (Figure 2D). The body of the injector and the head of the plunger were produced by machine-cutting. The plungers for the injector and loader, and the plate of the loader were made of nylon-12, using a three-dimensional printer. The tip tube of the injector, inner connecting tube for the plunger, loader tube, and sleeve tube were made of polypropylene which was produced by a straw maker (Shibase Co. Inc., Asakuchi City, Japan). The large-bore injector for thin films in large size up to 10 mm diameter had inner diameter of 1.7 mm with wall thickness of 0.2 mm, leading to outer diameter of 2.1 mm (Figure 2A). The small-bore injector for thin films in smaller size up to 7 mm diameter had inner diameter of 1.4 mm with wall thickness of 0.1 mm, leading to outer diameter of 1.6 mm (Figure 2B). A small-bore curved tip of the injector tube (Figure 2C and 2D) was produced by placing a curved guide wire into the polypropylene tube which went through the heating and cooling process. The best fit curvature of the tip was determined by testing the tips with different curvature to insert inside a human eyeball model through a hole placed at the location of the presumed pars plana. The plunger for the curved-tip tube consisted of a machine-cut polyphenylsulfone tip connected with press-fitting inner polypropylene tube to the nylon rod plunger. In contrast, the plunger for the straight-tip tube was simply made of the nylon rod. A coil spring was inserted along the plunger in the injector body. A circular dye-coupled film was pulled into a transparent tube of the loader with a commercial 25-gauge forceps (Grieshaber Revolution DSP 25Ga ILM Forceps, Alcon)

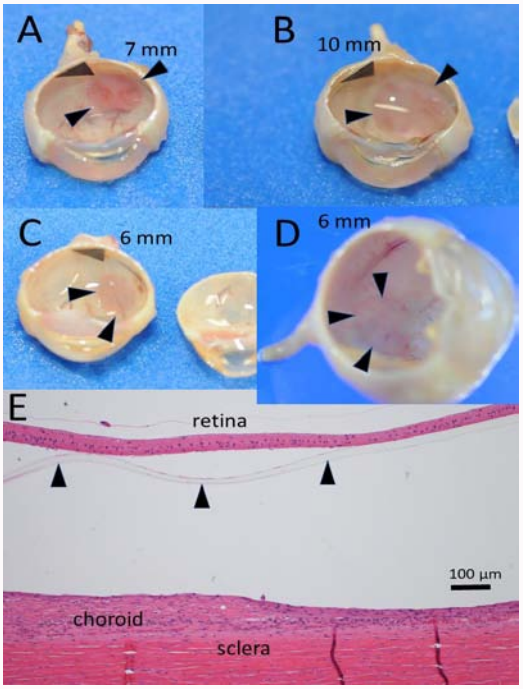

Figure 4: Autopsy one month after thin film implantation in sub-retinal space of rabbits' eyes. A) and B) Thin films in 7 mm and 10 mm diameter, respectively, inserted by straight-tip injector with large gauge (inner diameter 1.7 mm with wall thickness 0.2 mm, Figure 2A). C) and D) Thin films in 6 mm diameter inserted by straight-tip injector with small gauge (Figure 2B) and curved-tip injector with small gauge (inner diameter 1.4 mm with wall thickness 0.1 mm, Figure 2C), respectively. E) Paraffin section of the autopsy eye (the same as D) stained with hematoxylin-eosin. Note thin film (arrowheads) under the degenerative retina. The space between the retina and choroid is artefact in the process of fixation.

which was inserted into the tube from the opposite side (Figure 3A-3C). The loader tube was then joined with a sleeve to the tube tip of the injector (Figure 3D and 3E). The film in the loader was pushed with a plunger for the loader into the tip of the injector tube (Figure 3F and 3G). The loader tube with the sleeve was removed from the injector tube tip (Figure 3H), and the tube tip with the film was filled with intraocular irrigating solution, using 27-gauge blunt-end needle attached to a 2.5-mL disposable syringe (Figure 3I). The tube tip with the film was protected with a solution-filled cap (Figure 3J).

Surgical results

All circular dye-coupled films in different sizes were inserted successfully into the subretinal space by the large-bore and small-bore straight-tip injectors and small-bore curved-tip injector. The rolled films were pushed out from the injector tip into the subretinal space through a retinal hole. In the case of using large-bore or small-bore straight-tip injectors, the rolled films pushed out from the injector tip had to be touched by a light guide at the edge of the retinal hole to prevent the rolled film from coming out from the subretinal space. In the case of using the curved-tip injector, the rolled film pushed out from the injector tip stayed in the subretinal space with no additional aid (Figure 1L). After the insertion of the rolled films in the subretinal space, miotic change of the pupil was observed in almost all rabbit eyes even with frequent topical application of 0.5% tropicamide and 0.5% phenylephrine eye drops.

Pathological results

At the time of dissection one month after the implantation, all the films were confirmed to be located in the subretinal space of the rabbits' eyes (Figure 4A-4D). Retinal detachment was noted in one or two eyes in each group: sham surgery without film insertion, 7-mm film (Figure 4A) inserted by the large-bore straight-tip injector, 10 mm film (Figure 4B) inserted by the large-bore straight-tip injector, 6-mm film (Figure 4C) inserted by the small-bore straight-tip injector, and 6-mm film (Figure 4D) inserted by the small-bore curved-tip injector (Table 1). In pathological sections with hematoxylin-eosin stain, all eyes in different groups of rabbits showed mild to moderate levels of retinal degeneration, retinal pigment epithelial vacuolation, optic nerve atrophy, and ciliary body hemorrhage (Figure 4E). These pathological findings appeared to have no difference in the eyes which had film insertion, compared with the eyes with sham surgery. Infiltration with inflammatory cells was not noted in the retina and choroid.

Discussion

Since the previous report to describe the basic concept of a disposable injector for thin polyethylene films, continuous effort had been made to design and develop small-bore injectors, as described in this study [16]. We reached a polypropylene tube of inner diameter of 1.4 mm with wall thickness of 0.1 mm. The reason why the size was restricted to this smallest diameter was ascribed to technical limitation to make a polypropylene tube, according to accuracy and reproducibility at industrial standard in straw manufacturing. In the process of testing the straight-tip injector to insert the rolled film in rabbits' eyes, the rolled film which was pushed out of the tube tip naturally hit the retinal pigment epithelium at first. To make the rolled film stay in the subretinal space, an additional measure to push the rolled film at the edge of the retinal tear was required to change the direction of the rolled film in the subretinal space. Otherwise, the rolled film would tend to come out of the retinal tear into the vitreous cavity. In the case of using the straight-tip injectors, it was, therefore, desirable for the rolled film in the subretinal space to be touched with a light guide at the edge of the retinal tear after the film was ejected out of the tube tip. With the use of the curved-tip injector, the rolled film stayed in the subretinal space after the film was ejected out of the tube tip which was placed at the edge of the retinal tear. No additional action was required after simple action to put the tube tip of the injector into the retinal tear and to eject the rolled film out of the injector tip, as proved in this study. To make a plunger move smoothly inside the curved-tip polypropylene tube, separate part of

Table 1: Autopsy findings in rabbit eyes one month after the surgery.

Injector size and tip shape Inner diameter/Wall thickness/Outer diameter, tip shape	OUReP film diameter	Number of rabbits	Scleral incision width	Number of eyes with retinal detachment at autopsy
(Sham surgery)	-	3	3 mm	2
1.7 mm/0.2 mm/2.1 mm, straight tip	7 mm	3	3 mm	1
1.7 mm/0.2 mm/2.1 mm, straight tip	10 mm	3	3 mm	1
1.4 mm/0.1 mm/1.6 mm, straight tip	6 mm	5	2 mm	2
1.4 mm/0.1 mm/1.6 mm, curved tip	6 mm	4	2 mm	2

the tip of the plunger made of polyphenylsulfone was connected to the body of the plunger made of nylon *via* a small-bore polypropylene tube. The connection between the parts was accomplished by press-fit insert to avoid using adhesives. In parallel with this study, polypropylene tube and plunger tips were tested to have no toxicity in *in-vitro* cytotoxicity test, ocular surface irritation test in rabbits, and skin sensitization test in Guinea pigs for biological evaluation of medical devices, based on International Standard ISO 10993 (data not shown).

In animal studies using rabbits' eyes, pathological findings at the dissection one month after the surgery were not different among different conditions. Furthermore, the rate of retinal detachment was basically the same among different groups with film implantation by the large-bore and small-bore straight-tip injectors and small-bore curved-tip injectors. It should be noted that retinal detachment was caused at the similar rate even in the eyes with sham surgery. These facts suggest that vitrectomy procedure in itself would cause these changes in the rabbits' eyes. In other words, technical easiness in handling the injectors to insert the film into the subretinal space would not influence the pathological outcome in the rabbits' eyes. In our previous studies, the dye-coupled films were grasped with a 25-gauge forceps and implanted in the monkey eyes [15], rabbits' eyes [14], and canine eyes to prove the safety of the films as well as the safety of surgical procedures at vitrectomy [13]. In the monkey study [15], the efficacy of the dye-coupled film to improve the vision was also proven by visual evoked potential recovery in the eyes with macular degeneration. No retinal detachment was noted for 6 months in all the monkey eyes with the dye-coupled film implantation [15]. In contrast with the monkey study [15], retinal detachment even in rabbits' eyes with sham surgery in the present study would be ascribed to the propensity in rabbits for inducing inflammation [23]. It should be also emphasized in the present study that miosis of the pupil during the surgery after the insertion of the dye-coupled film in almost all rabbits' eyes would be attributed to the inflammatory propensity in rabbits. In future perspectives, the dye-coupled film (OUReP) and curved-tip disposable OUReP injector as a surgical set will be provided to Okayama University Hospital for an investigator-initiated clinical trial which will enroll patients who have lost the vision by retinitis pigmentosa [24,25].

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