Original Report　　原　著

Novel disposable injector (OUReP Injector) tested in experimental aphakic eyes of rabbits for subretinal implantation of Okayama University-type retinal prosthesis (OUReP)

Toshihiko MATSUO[1)], Tetsuya UCHIDA[2)], Koichiro YAMASHITA[2)], Chie MATSUO[3)], Yusuke KAWAKAMI[4)], Toshiya HITOMI[4)], Kanji TAGA[4)], Tatsuya SANADA[4)], Yusuke YAMASHITA[5)], Koichi KURAMOTO[6)]

1) Ophthalmology, Okayama University Medical School and Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama-shi, Okayama 700-8558, Japan
2) Polymer Materials Science, Okayama University Faculty of Engineering, Graduate School of Natural Science and Technology, Okayama-shi, Okayama 700-8530, Japan
3) Orthodontist, Okayama-shi, Okayama 700-0015, Japan
4) Minori Industry Co., Ltd., Soja-shi, Okayama 719-1154, Japan
5) Shin Nippon Biomedical Laboratories, Ltd., Kagoshima-shi, Kagoshima 891-1394, Japan
6) Okayama University Organization for Research Promotion and Collaboration, Okayama-shi, Okayama 700-8558, Japan

Correspondence to Toshihiko Matsuo, MD, PhD, Department of Ophthalmology, Okayama University Medical School and Graduate School of Interdisciplinary Science and Engineering in Health Systems, 2-5-1 Shikata-cho, Okayama City 700-8558, Japan.
Phone: +81-86-235-7297, Fax: +81-86-222-5059
e-mail: matsuot@cc.okayama-u.ac.jp

Summary

Okayama University-type retinal prosthesis (OUReP™) is a photoelectric dye-coupled polyethylene film which generates electric potential in response to light and stimulates nearby neurons. This study reports a novel disposable injector to insert the dye-coupled film in subretinal space of the eye by vitreous surgery in rabbits. The injection system composed of two separate parts, injector and loader. A circular film in 5-10 mm diameter was first 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. Bleb retinal detachment was induced in 8 experimental aphakic eyes of rabbits 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 film was inserted from 3 mm-wide scleral incision into vitreous and then into subretinal space. The film was released into subretinal space by pushing the plunger with index finger while the injector body was held with thumb and other fingers. The plunger was pushed back automatically by a coil spring inside the injector. Dissection after surgeries confirmed successful implantation of 4 films in 5 mm diameter and 4 films in 7 mm diameter into subretinal space of each rabbit eye. The film insertion by the injector was technically feasible at vitreous surgery in rabbit eyes.

Received: December 30, 2017
Accepted: January 31, 2018
Keywords: dye-coupled thin film retinal prosthesis, injector, photoelectric dye, rabbit, vitrectomy

岡山大学方式人工網膜 (OUReP) を網膜下に植込む使い捨て注入器 (OUReP Injector) 作成とウサギ模擬試験

松尾俊彦[1)]、内田哲也[2)]、山下功一郎[2)]、松尾智江[3)]、川上雄祐[4)]、人見敏哉[4)]、多賀幹治[4)]、眞田達也[4)]、山下祐介[5)]、蔵本孝一[6)]

1) 岡山大学大学院ヘルスシステム統合科学研究科眼科学分野
(700-8558) 岡山市北区鹿田町2-5-1
2) 岡山大学大学院自然科学研究科高分子材料学分野
(700-8530) 岡山市北区津島中3-1-1
3) 歯科医師
(700-0015) 岡山市北区京山2-3-3
4) 三乗工業株式会社
(719-1154) 総社市井尻野100
5) 株式会社新日本科学
(891-1394) 鹿児島市宮之浦町2438
6) 岡山大学研究推進産学官連携機構
(700-8558) 岡山市北区鹿田町2-5-1

連絡責任者：松尾俊彦
(700-8558) 岡山市北区鹿田町2-5-1
岡山大学大学院ヘルスシステム統合科学研究科眼科学分野
電話: 086-235-7297　Fax: 086-222-5059
E-mail: matsuot@cc.okayama-u.ac.jp

要　　約

岡山大学方式の人工網膜 (OUReP) は光電変換色素分子をポリエチレン薄膜表面に共有結合した世界初の新方式の色素結合薄膜型である。光を受けて表面電位変化を生じ近傍の神経細胞の活動電位を惹起する。これまでの動物試験ではこの色素結合薄膜型人工網膜を20Gの眼内鑷子で掴んで網膜下に挿入していた。今回の報告では色素結合薄膜を網膜下に挿入する使い捨て注入器 (OUReP Injector) を開発してウサギ模擬試験を行った。人工網膜注入器は色素結合薄膜を注入器先端から装填する先込め方式である。注入器本体と先込め器から構成される。注入器本体の先端は内径2mmの透明なチューブで、その中を注入器の押し棒が動き、押し棒は指を離すと注入器内部の押し棒周囲のコイル状金属バネによって自然に戻る。先込め器は平板上に内径2mmの透明チューブが固定してある。直径5-10mmの円形の色素結合薄膜を先込め器平板の切込み溝に立てて、溝とは反対側のチューブ口から 25G眼内鑷子を突っ込み、切込み溝に立つ薄膜を掴んでチューブ内に引っ張り込む。先込め器のチューブと注入器先端のチューブとを透明な外筒チューブで連結して、先込め器チューブ内にある薄膜を注入器本体の先端チューブ内に先込め器用の押し棒で押し込む。先込め器を連結外筒チューブと一体で注入器先端チューブから外す。薄膜が装填された注入器先端チューブ中を27G 鈍針からの眼内灌流液で満たす。ウサギの実験的無水晶体眼8眼を使って注入器の動作性を確認する模擬手術を行った。25Gシステムの硝子体手術で38Gポリイミド針を使って網膜下に眼内灌流液を注入して網膜剥離を作成した。網膜凝固によって網膜剥離部に網膜裂孔を作成し、3mmの強膜創から人工網膜注入器を硝子体中に挿入し、その先端を網膜下に進めて薄膜を押し出した。その後、網膜下液を吸引して網膜を復位させ網膜裂孔周囲をレーザー凝固し、シリコンオイルを硝子体中に注入して手術を終えた。剖検して網膜下に色素結合薄膜が存在することを全例で確認した。この試験によって OUReP Injector の技術的有用性が示された。

Introduction

Patients with hereditary retinal diseases, such as retinitis pigmentosa,[11,19] have lost vision by death of photoreceptor cells, but the other retinal neurons, which send axons to the brain, remain alive.[8] Spontaneous retinal dystrophies, similar to the disease in human, have been also described in animals such as rats[1-3] and dogs.[18] The rationale of retinal prostheses is to stimulate surviving retinal neurons such as ganglion cells and bipolar cells with artificial devices in response to light,[8] and to expect these living retinal neurons to send electric signals as action potential to the brain.

The modality of retinal prosthesis which is available at the market utilizes a multielectrode array.[6] Camera-captured image is disintegrated to 60 pixels, and the electric current, corresponding to grayscale tone in each pixel, is outputted from 60 electrodes to stimulate the retinal living neurons in Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA, USA). Surgical implantation of the multielectrode array with wiring connection indeed requires sophisticated techniques.

Okayama University-type retinal prosthesis (OURePTM) is designed as a novel system of retinal prosthesis which is composed of a photoelectric dye-coupled thin film.[1-3,20-23] Stable photoelectric dye molecules with absorption spectrum of visible light[7,9,12,17] were chemically coupled to polyethylene film surface. The dye-coupled film generates electric potential in response to light and stimulates nearby neuronal cells to induce action potential.[5] The dye-coupled film functions as a light sensor and a potential generator in subretinal space of the eye, and thus replaces the function of dead photoreceptor cells in retinal dystrophy.[11,19] Electric signals which are generated in the living retinal bipolar cells and ganglion cells in response to light are sent to the brain through the axons of retinal ganglion cells as action potential along optic nerve fibers.[8]

The dye-coupled film is a soft and thin sheet which would be rolled up and inserted in subretinal space of the eye by vitrectomy.[13,14] In our previous animal experiments, the dye-coupled films were grasped with a 20-gauge forceps and implanted subretinally in canine eyes,[14] rabbit eyes,[15] and monkey eyes.[16] Film implantation, using a forceps, was a technically limiting step in surgical procedures. In this study, a novel disposable injector was designed for subretinal dye-coupled film implantation to overcome a technical barrier, and was tested in 8 experimental aphakic eyes of rabbits for technical feasibility at vitreous surgery.

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.[2,21,23] Dye-coupled films were manufactured in quality management system at a clean-room facility in Okayama University Incubator.

Animals

Normal male white rabbits (Kbl:JW, specific pathogen free, Kitayama Labes Co., Ina City, Japan) at the age of 15 weeks were used in this study. The initial model of the injector was tested in 4 eyes of 3 rabbits on one day, and the modified model was tested in 4 eyes of 2 rabbits on the other day. After dye-coupled film implantation, all animals were sacrificed by bleeding with overdose of intravenous pentobarbital sodium (0.7-0.9 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, and dissected for photography. 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 (IACUC736-006 and IACUC736-007).

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 Lifescience, 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 one side down for the other eye surgery, and covered with a surgical drape. Topical anesthesia was further obtained with 4% lidocaine (Xylocaine Ophthalmic Solution, AstraZeneka, London, UK). The surgery was done under a surgical microscope (OPMI VISU150, Carl Zeiss Meditec, Tokyo, Japan) with a surgical machine (Constellation Vision System, Alcon Laboratories, Inc., Fort Worth, TX, USA). Anterior capsulectomy (Fig. 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).[10] Phacoemulsification and aspiration of the lens in the capsular bag (Fig. 1B) was done through a 2.4 mm-wide corneal incision 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 into the vitreous through the sclera 2 mm from the limbus on the superior to temporal side within 120 degrees of meridian (Fig. 1C, 1D). The presence of a large vascularized nictitating membrane on nasal side of the conjunctiva limited the surgical area used for placing trocars.

The wide-field fundus was viewed with a +128-diopter front lens by Resight 500 fundus viewing system (Carl Zeiss Meditec). First, posterior capsulectomy and core vitrectomy was done under irrigation with a 25-gauge cannula placed at the middle trocar on the superior side (Fig. 1D). Retinal detachment was made by infusing irrigation solution (BSS-Plus Intraocular Irrigating Solution, Alcon) into the subretinal space with a 38-gauge polyimide tip (PolyTip Cannula 25G/38G, MedOne 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 (Fig. 1E, 1F, 1G). A retinotomy was made by 25-gauge diathermy (Grieshaber Diathermy Probe DSP 25Ga, Alcon) at the edge of retinal detachment (Fig. 1H). A 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 (Fig. 1I) was inserted through the scleral incision into the vitreous (Fig. 1J) and then under the detached retina via a retinotomy (Fig. 1K). The film was released into the subretinal space (Fig. 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.

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 (Fig. 1M). Laser photocoagulation was applied around the retinal tear caused by retinotomy, and silicone oil (polydimethylsiloxane, Silikon 1000, Alcon) was injected into vitreous cavity by the VFC syringe (Fig. 1N). Trocars were removed, and the conjunctiva was sutured with 8-0 Vicryl suture (Fig. 1O).

Results

Design of injector

The injection system composed of two separate parts, an injector with a plunger and a loader tube fixated on the plate (Fig. 2A). The body of the injector with the plunger, and the plate of the loader were made of nylon-12, using a three-dimensional printer. In the initial model, the tip tube of the injector, and the loader tube were made of perfluoroalkoxy fluorine resin (PFA) with 0.5 mm wall thickness which was commercially available. The sleeve was also a commercially available tube made of PFA. The modified model (Fig. 2A) consisted of PFA tubes with 0.3 mm wall thickness. The tip of the injector tube was cut obliquely at 45 degrees in the initial model, and was changed to the dull angle of 60 degrees in the modified model. The inner diameter of the injector tube was 2.0 mm, and the outer diameter of the plunger was set at 1.95 mm or greater since the thickness of the dye-coupled film was 0.03 mm. A coil spring was inserted along the plunger in the injector body.

A circular dye-coupled film in the diameter of 5-10 mm was first placed in the groove with 0.5 mm width on the loader plate (Fig. 2B). The groove on the plate for placing a dye-coupled film was V-shaped in the initial model, while U-shaped in the modified model. The position of the groove was not central relative to the loader tube in the initial model while the groove was in central alignment with the tube in the modified model. The film was pulled into a transparent tube of the loader with a commercial 25-gauge forceps (Grieshaber Revolution DSP 25Ga ILM Forceps, Alcon), which was inserted into the tube from the opposite side of the groove where the film was placed (Fig. 2C, 2D, 2E, 2F). The loader tube was then joined with a sleeve to the tube tip of the injector. The film in the loader was pushed with a plunger for the loader into the tip of the injector tube (Fig. 2G, 2H, 2I, 2J). The loader with the sleeve was removed from the injector tube tip, 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 (Fig. 2K). Both the initial model and the modified model worked well with films in diameter, ranging from 5 mm to 10 mm, in repeat testing on bench.

Complications during surgery

The four eyes of 3 rabbits were used for testing of 4 initial-model injectors on one day. In the study plan, both eyes (4 eyes) of 2 rabbits were scheduled to be used for testing. Surgical time in the right eye of the first rabbit became longer up to 90 min, and thus, the left eye was not used for surgery due to an anesthetic problem. The trocars were inserted over the conjunctiva in the right eye of the first rabbit, and both eyes of the second rabbit. An only and major surgical complication was spontaneous drop-out of the trocars which were inserted over the conjunctiva through the sclera into the vitreous. When the trocar with an infusion cannula, serving fluid irrigation or air infusion, dropped out, rapid reinsertion of the trocar was mandatory to maintain the intraocular pressure.

In the testing of 4 initial-model injectors, drop-out of trocars for instrument insertion resulted in longer duration of surgery but did not give rise to any complications in the right eye of the first rabbit. In contrast, drop-out of the trocar with infusion cannula resulted in serious complications: subretinal air infusion in the right eye of the second rabbit and vitreous hemorrhage in the left eye of the second rabbit. To avoid this complication, the conjunctiva was opened and trocars were inserted directly through the sclera in

the right eye of the third rabbit. In addition, the tube of the injector did not move smoothly through the scleral incision. So the tube was coated with silicone oil, used for vitreous filling, and made the tube lubricant at testing in the right eye of the third rabbit (Fig. 2L). After the surgery, dissection of the enucleated eyes showed the dye-coupled films in the subretinal space.

In the testing of 4 modified-model injectors on the other day, no complication was noted in both eyes (4 eyes) of 2 rabbits in which the trocars were directly inserted through the bare sclera after conjunctival incision (Fig. 1C, 1D). Silicone oil as a lubricant was used for coating of the tube tip (Fig. 2L). After the surgery, dissection of the enucleated eyes showed the dye-coupled films in the subretinal space (Fig. 3A, 3B).

Evaluation of injector

Overall, the injectors of the initial and modified models worked as expected to release the film into the subretinal space. Four injectors of the initial model were tested with dye-coupled films in 5 mm diameter, resulting in successful release of the films in all 4 eyes of rabbits. Four injectors of the modified model were tested with dye-coupled films in 7 mm diameter: 3 injectors worked, as expected, to release the films in 3 eyes of rabbits. In the remaining one eye at the third surgery tested with the film in 7 mm diameter, the film in the tube tip of one injector could not be released at the first attempt since the plunger went through inside the rolled film which touched so closely the inner wall of the tube tip. In this case, the rolled film inside the tube tip was movable with a forceps and was released successfully after the location of the film was changed so not to contact closely with the inner wall of the tube. After the experiment, the diameter of each plunger in the modified model was measured: 1.95 mm for the unsuccessful injector, and 1.97-1.98 mm for the three successful injectors, in relation with 2.0 mm internal diameter of the injector tube.

Discussion

The goal of this study is to prove the usability of OUReP Injector in rabbit eyes at the setting of vitrectomy. Rabbits have been frequently used as a model animal to test ophthalmic techniques. In this study, we used 25-gauge vitrectomy and wide-viewing front lens system which is now the standard for vitrectomy in human eye surgeries. Recently, technical methods for 20-gauge vitrectomy in rabbits have been summarized in the literature.[4] This study showed technical feasibility of 25-gauge vitrectomy and wide viewing system in rabbit eyes.[15] Based on the surgeon's impression, insertion of the films appeared to be technically easy by the use of the injector, compared with film insertion with a forceps in the preceding studies.[14,15] In addition, films in a larger size (7 mm diameter), compared with the preceding studies, could be inserted into subretinal space of rabbit eyes in the present study.

A major problem in 25-gauge vitrectomy in rabbit eyes was the tendency of trocars to get out of place spontaneously. Initially in the experiments,[15] 25-gauge trocars were inserted over the conjunctiva through the sclera into the vitreous, as are done in human eyes. Mainly due to the thinness and weakness of the scleral tissue, vitreous fluid leaked out around the trocars and was accumulated beneath the conjunctiva. Ballooned subconjunctival fluid accumulation then pushed the head of trocars, especially the trocar connected to the infusion cannula, and made the trocars get out of place. To overcome this serious complication regarding drop-out of the infusion cannula, the conjunctiva was opened first and the trocars were inserted directly though the sclera into the vitreous. Under the circumstances, the trocar with the infusion cannula was stable during the surgery. In case of other trocars for instrument insertion which got out of place, scleral holes made by trocar insertion were visible and instruments could be inserted through these scleral holes directly into the vitreous.

The OUReP Injector is unique at the point that the dye-coupled film is inserted into the injector from its tip through the removal loader. This tip-front loading system avoided the film from being trapped along the tube. Another point is oblique cut of the injector tip at dull angle of 60 degrees. The dull angle allowed the tip end to be inserted in the minimum length into the subretinal space when the film was pushed out from the tip end. In the initial model with a sharper angle (45 degrees) of the tube tip, the tip end had to be inserted in the longer length under the subretinal space, and thus, the tip end would hit the retinal pigment epithelium at a higher rate, compared with the dull-angled end. The basic design of the injector has been thus settled with the present modified form.

One problem which has remained to be solved is to make the injector tube move smoothly through as small scleral incision as possible. In the present experiments, the tube was coated with silicone oil, used for vitreous filling, to make the tube surface lubricant. The silicone oil-coating allowed the surgeon to insert the injector through the tight scleral incision smoothly and to bring the tip end precisely at the desired position under the subretinal space. The deformation of the eye globe, caused by pressure on the scleral incision, was not induced at the insertion of the tube, and thus, the intraocular pressure was maintained at the constant level. The stable condition of the eye globe is mandatory to advance the tube tip safely in the subretinal space while care is taken not to hit the retinal pigment epithelium with the tip end. The tube surface modification to make the tube move smoothly through the tight scleral incision will be achieved by surface coating of the tube.

The design of the injector will be further refined as follows. The thinning of the injector tube wall, up to 0.1 mm, can be accomplished by the use of different polymers, such as polypropylene, for the injector tube tip. In addition, the plunger end of the injector will be ballooned in shape to fit more closely with the inner wall

of the injector tube so as to avoid the plunger from going through inside the rolled film, as noted in this study. The refinement is now in progress to manufacture the final version of the injector.

In conclusion, we designed and developed a novel disposable injector to insert the dye-coupled film into the subretinal space of the eye. The film insertion with the injector was technically feasible at vitreous surgery in rabbit eyes. The OURePInjector is a novel medical device, designated as Class II in Japan, and would be tested in a clinical trial as a first-in-human feasibility study of the dye-coupled film, OURePThe approval of the OURePInjector as a medical device (Class II) is in consultation with Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. In future, the OURePinjector would be also used in vitreous surgeries for dogs with retinal dystrophies[18] at veterinary clinics.

Acknowledgments

We thank staffs in Shin Nippon Biomedical Laboratories, Ltd., Kagoshima City, Japan, for helping us conduct experiments in rabbits. We also thank Dr. Toshinori Furukawa in Kurashiki University of Science and the Arts, Dr. Shigiko Takei and Dr. Daisuke Ido in Ina Research, Inc., for their advice in surgeries. This study was supported by a grant for the Translational Research Network Program from the Japan Agency for Medical Research and Development (AMED).

References

1. Alamusi, Matsuo, T., Hosoya, O. and Uchida, T. (2017): Visual evoked potential in RCS rats with Okayama University-type retinal prosthesis (OURePTM) implantation. *J. Artif. Organs* **20**: 158-165.
2. Alamusi, Matsuo, T., Hosoya, O. et al. (2015):Vision maintenance and retinal apoptosis reduction in RCS rats with Okayama University-type retinal prosthesis (OURePTM) implantation. *J. Artif. Organs* **18**: 264-271.
3. Alamusi, Matsuo, T., Hosoya, O. et al. (2013): Behavior tests and immunohistochemical retinal response analyses in RCS rats with subretinal implantation of Okayama-University-type retinal prosthesis. *J. Artif. Organs* **16**: 343-351.
4. Al-Nawaiseh, S., Thieltges, F., Liu, Z. et al. (2016): A step by step protocol for subretinal surgery in rabbits. *J. Vis. Exp.* **13**(115): doi: 10.3791/53927.
5. Huang, F., Bladon, J., Lagoy, R. C. et al. (2015): A photosensitive surface capable of inducing electrophysiological changes in NG108-15 neurons. *Acta. Biomater.* **12**: 42-50.
6. Humayun, M. S., Dorn, J. D., da Cruz, L. et al. (2012): Interim results from the international trial of Second Sight's visual prosthesis. *Ophthalmology* **119**: 779-788.
7. Liu, S., Matsuo, T., Hosoya, O. et al. (2017): Photoelectric dye used for Okayama University-type retinal prosthesis reduces the apoptosis of photoreceptor cells. *J. Ocul. Pharmacol. Ther.* **33**: 149-160.
8. Loewenstein, J. I., Montezuma, S. R. and Rizzo, J. F. III. (2004): Outer retinal degeneration: an electronic retinal prosthesis as a treatment strategy. *Arch. Ophthalmol.* **122**: 587-596.
9. Matsuo, T. (2003): A simple method for screening photoelectric dyes towards their use for retinal prostheses. *Acta Med. Okayama* **57**: 257-260.
10. Matsuo, T. (2014): Intraocular lens implantation in unilateral congenital cataract with minimal levels of persistent fetal vasculature in the first 18 months of life. *SpringerPlus* **3**: 301.
11. Matsuo, T. and Morimoto, N. (2007): Visual acuity and perimacular retinal layers detected by optical coherence tomography in patients with retinitis pigmentosa. *Br. J. Ophthalmol.* **91**: 888-890.
12. Matsuo, T., Dan-oh, Y. and Suga, S (Inventors). (2006): Agent for inducing receptor potential. Assignee: Okayama University. United States Patent. Patent No.: US 7,101,533 B2. Date of Patent: Sep. 5, 2006.
13. Matsuo, T., Uchida, T. and Takarabe, K. (2009): Safety, efficacy, and quality control of a photoelectric dye-based retinal prosthesis (Okayama University-type retinal prosthesis) as a medical device. *J. Artif. Organs* **12**: 213-225.
14. Matsuo, T., Uchida, T., Nitta, M. et al. (2017). Subretinal implantation of Okayama University-type retinal prosthesis (OURePTM) in canine eyes by vitrectomy. *J. Vet. Med. Sci.* **79**: 1939-1946.
15. Matsuo, T., Uchida, T., Yamashita, K. et al. (2018): Visual evoked potential in rabbits' eyes with subretinal implantation by vitrectomy of Okayama University-type retinal prosthesis (OURePTM). *J. Vet. Med. Sci.* **80**: 247-259.
16. Matsuo, T., Uchida, T., Sakurai, J. et al. (2018): Visual evoked potential recovery by subretinal implantation of photoelectric dye-coupled thin film retinal prosthesis (OUReP) in monkey eyes with macular degeneration. *Artif. Organs* **42**: E186-E203.
17. Okamoto, K., Matsuo, T., Tamaki, T. et al. (2008): Short-term biological safety of a photoelectric dye used as a component of retinal prostheses. *J. Artif. Organs* **11**: 45-51.
18. Petersen-Jones, S.M. and Komaromy, A.M. (2015): Dog models for blinding inherited retinal dystrophies. *Hum. Gene Ther. Clin. Dev.* **26**: 15-26.
19. Tamaki, M. and Matsuo, T. (2011): Optical coherence tomographic parameters as objective signs for visual acuity in patients with retinitis pigmentosa, future candidates for retinal prostheses. *J. Artif. Organs* **14**: 140-150. Erratum **14**: 385.
20. Tamaki, T., Matsuo, T., Hosoya, O. et al. (2008): Glial reaction to photoelectric dye-based retinal prostheses implanted in the subretinal space of rats. *J. Artif. Organs* **11**: 38-44.

21. Uchida, T., Ishimaru, S., Shimamura, K. et al. (2005): Immobilization of photoelectric dye on the polyethylene film surface. *Mem. Fac. Eng. Okayama Univ.* **39**: 16-20.
22. Uji, A., Matsuo, T., Uchida, T. et al. (2006): Intracellular calcium response and adhesiveness of chick embryonic retinal neurons to photoelectric dye-coupled polyethylene films as prototypes of retinal prostheses. *Artif. Organs* **30**: 695-703.
23. Uji, A., Matsuo, T., Ishimaru, S. et al. (2005): Photoelectric dye-coupled polyethylene film as a prototype of retinal prostheses. *Artif. Organs* **29**: 53-57.

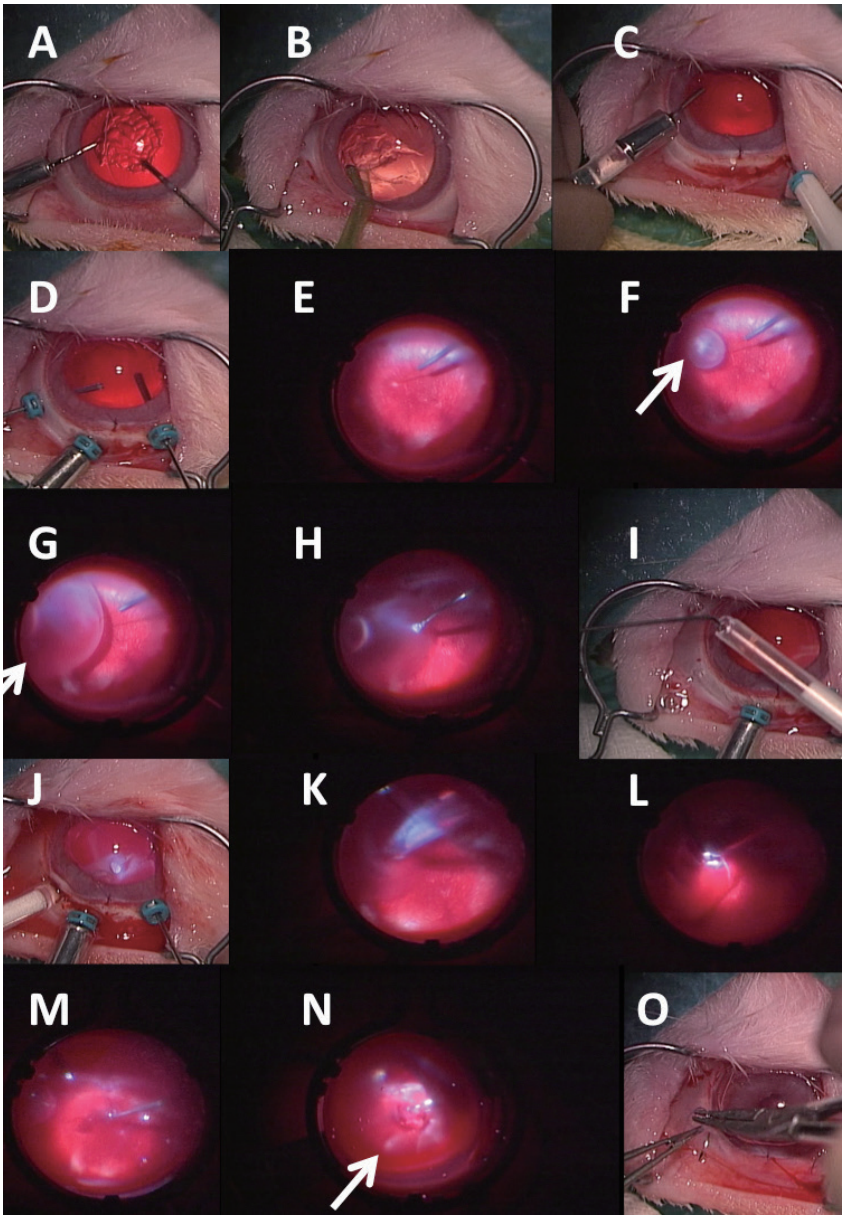

Fig. 1. Surgical procedures to implant retinal prosthesis (OURePTM) with OURePInjector as a modified model. **A.** Lens anterior capsule is cut with 25G vitreous cutter under irrigation with 25G infusion cannula in the anterior chamber. **B.** Lens nucleus and cortex is aspirated with phacoemulsification 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. **D.** Posterior capsule is cut with vitreous cutter. **E.** After vitreous gel has been cut, subretinal fluid infusion is started with 38G tip. **F.** Bleb retinal detachment (arrow) is made by 38G tip infusion of intraocular irrigating solution. **G.** Bleb (arrow) is enlarged with further infusion. **H.** A retinal tear (white spot) is made by retinal coagulation with 25G bipolar diathermy. **I.** After scleral incision is made, OUReP injector tip with 7-mm diameter circular film is filled again with irrigating solution with a 27-gauge blunt-end needle. **J.** Injector is inserted from scleral incision into vitreous. **K.** Injector tip is inserted into subretinal space through a retinal tear. **L.** Plunger of the injector is pushed to release the film into subretinal space. **M.** Fluid-air exchange in vitreous cavity is done with 25G vitreous cutter in aspiration mode. **N.** After retinal reattachment with air in vitreous cavity, laser coagulation is applied around the retinal tear and silicone oil is injected in vitreous cavity with 25G tip. Note subretinal dye-coupled film (arrow). **O.** Scleral and conjunctival incision are sutured and trocars are removed.

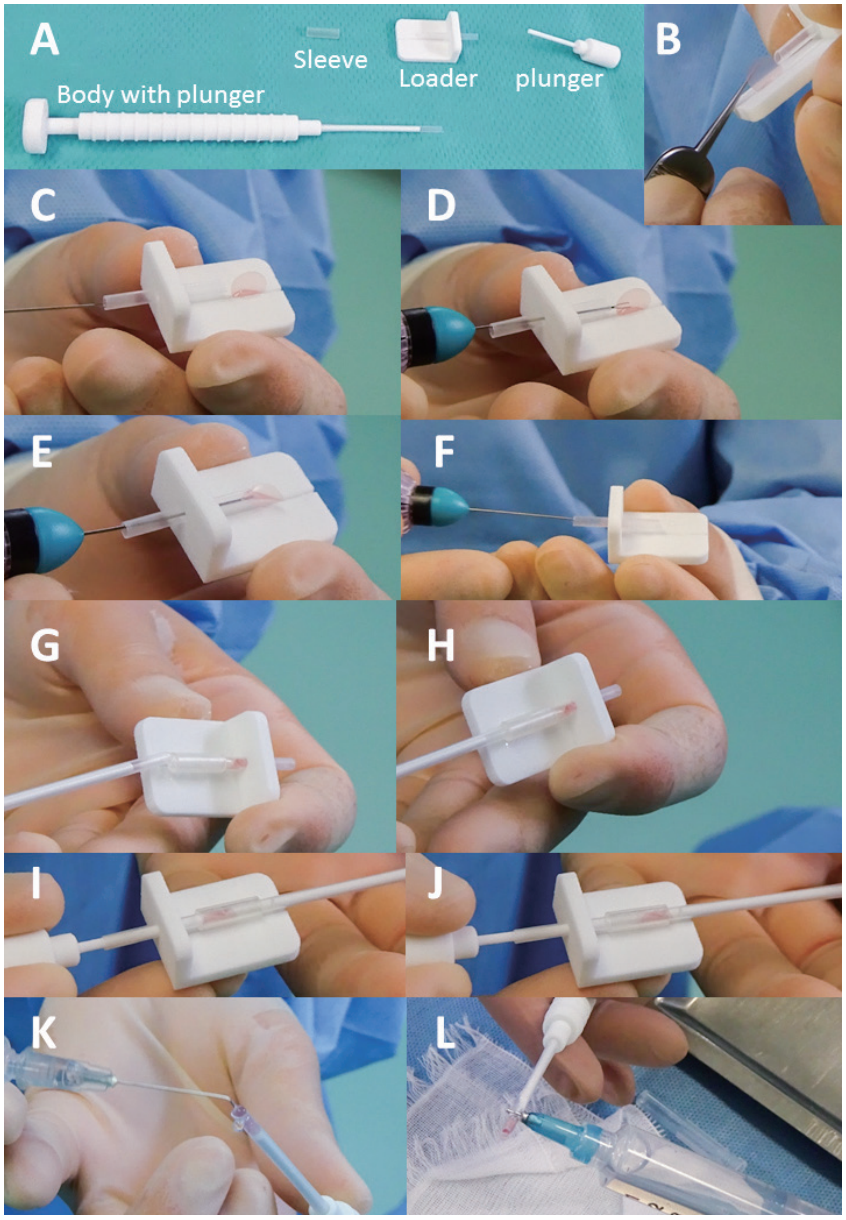

Fig. 2. **A.** Injector body with plunger, sleeve, and loader plate with plunger as a modified model. **B.** Circular dye-coupled film in 7-mm diameter is placed in 0.5-mm wide U-shaped groove on the loader plate. **C, D, E, and F.** The film is pulled into a transparent tube of the loader with a commercial 25-gauge forceps (Grieshaber Revolution DSP 25Ga ILM Forceps, Alcon), which is inserted into the tube from the opposite side of the groove where the film is placed. **G, H, I, and J.** The loader tube is joined with a sleeve to the tube tip of the injector. The film in the loader is pushed with a plunger for the loader into the tip of the injector tube. **K.** After the loader with the sleeve is removed from the injector tube tip, 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. **L.** Injector tip surface is lubricated with silicone oil.

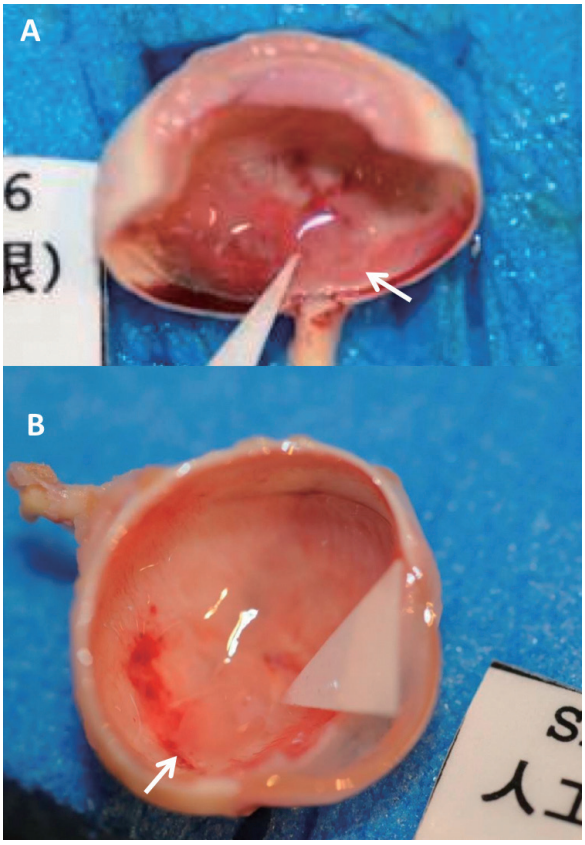

Fig. 3. Pathological dissection of the eyes after enucleation and fixation, showing dye-coupled films placed in the subretinal space (arrows). **A.** 5-mm diameter film inserted by the initial-model injector in the right eye of third rabbit. **B.** 7-mm diameter film inserted by the modified-model injector in the left eye of second rabbit.