Glaucoma

Grooved Glaucoma Drainage Devices That Continuously Deliver Cyclosporine A Decrease Postsurgical Scar Formation in Rabbit Eyes

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PURPOSE. To study the functional outcomes of filtration surgery by implanting improved glaucoma drainage devices (GDDs) comprising surface grooves and a composite coating of cyclosporine A (CsA) and PLGA in experimental rabbit eyes.

METHODS. Improved GDDs were designed and prepared by modifying normal GDD with surface grooves and a CsA-PLGA composite coating. Normal GDDs, grooved GDDs (G-GDDs), and G-GDDs with a CsA-PLGA composite coating (CsA@G-GDD) were implanted into 18 rabbit eyes (six eyes per group). The intraocular pressure (IOP), bleb survival time, bleb morphology, and anterior chamber reactions were assessed statistically among the three groups. Bleb morphology was quantified using the Indiana Bleb Appearance Grading Scale. Anterior chamber radiography was performed to check whether the filtrating pathway was blocked, and determine the drainage time and diffusion area of the contrast agent. Hematoxylin and eosin staining and immunohistochemistry were conducted to assess how the GDDs slowed or prevented scar formation.

RESULTS. The improved GDDs were successfully prepared and implanted in 18 rabbit eyes without severe surgical complications. Bleb survival time was significantly longer and IOP was significantly lower in the G-GDD and CsA@G-GDD groups compared with the GDD group (all, P < 0.001). Blesbs were significantly higher in the CsA@G-GDD group than in the GDD and G-GDD groups (P = 0.003). Anterior chamber radiography revealed more unobstructed filtration channels in the CsA@G-GDD group than in the GDD group (P = 0.032). Postsurgical scar formation was less extensive in the G-GDD and CsA@G-GDD groups than in the GDD group.

CONCLUSIONS. Compared with the normal GDDs, G-GDDs with a CsA-PLGA coating inhibited postsurgical scar formation and improved the surgical success rate, and might represent an alternative to existing glaucoma filtration devices.

Keywords: glaucoma drainage devices, cyclosporine A, groove, filtration surgery, scar formation

Glaucoma is characterized by elevated intraocular pressure (IOP) and frequently causes optic neuropathy. If left untreated, it causes chronic progressive degeneration of retinal ganglion cells and visual field loss. The treatment of glaucoma typically begins with topical medications and then filtering surgeries. Glaucoma filtration surgery seeks to achieve incomplete healing to allow the aqueous humor to escape the eye, unlike other surgical procedures in which complete wound healing is desired. Unfortunately, IOP often increases after surgery owing to scar formation in the wound field. The success rate of trabeculectomy was reported to be 64.7% over 5 years in eyes with open-angle glaucoma. In complicated cases, implantation of a GDD was associated with a success rate of 76.9% to 87.5% over 1 year in eyes with refractory glaucoma, and success rates of 73.1% over 1 year and 20.6% over 5 years in eyes with neovascular glaucoma. The wound healing process after surgery is characterized by increased secretion of growth factors and proinflammatory factors that promote the proliferation of fibroblasts and collagen deposition, which contribute to scar formation and stenosis of the drainage pathway. These changes may lead to uncontrollable IOP and ultimately failure of the filtration surgery in majority of cases.

Mitomycin C (MMC) and 5-fluorouracil are antimetabolic agents that are usually administered to prevent scar formation after glaucoma surgery. However, the high dose of MMC and short-term exposure during surgery can lead to focal toxicity...
after glaucoma surgery. Moreover, we thought that modifying for continuous drug delivery in order to prevent scar formation with CsA and poly (lactic-co-glycolic acid) polymer (CsA-PLGA) recently published paper, we developed a novel GDD coated effective concentration for GDD surface. The composite coating released CsA at a safe and an composite CsA-PLGA coating can also be applied to the grooved its surface and prepared and tested the modified GDDs. A recent study, we designed a GDD with a radial groove pattern on the drainage function and antiscar effects of the GDD. In our and poor long-term outcomes. Cyclosporine A (CsA), an immunosuppressant, is less toxic than MMC and 5-fluorouracil, and it was shown to prevent scar formation after glaucoma surgery. In order to reduce focal drug toxicity and improve the long-term effects of these drugs, continuous drug delivery may be essential.

Several drug delivery systems capable of sustained release of CsA have been developed, including hydrogel contact lens, microspheres, nanoparticles, sol-gel, and micelles, some of which may also be used in combination. In our recently published paper, we developed a novel GDD coated with CsA and poly (lactic-co-glycolic acid) polymer (CsA-PLGA) for continuous drug delivery in order to prevent scar formation after glaucoma surgery. Moreover, we thought that modifying the GDD—with surface grooves, for example—might enhance the drainage function and antiscar effects of the GDD. In our recent study, we designed a GDD with a radial groove pattern on its surface and prepared and tested the modified GDDs. A composite CsA-PLGA coating can also be applied to the grooved GDD surface. The composite coating released CsA at a safe and an effective concentration for ≥12 weeks. Therefore, we developed grooved GDDs (G-GDDs) with or without the CsA-PLGA coating, as well as normal GDDs as a control. These GDDs were implanted into rabbit eyes. Intraocular pressure, bleb survival time, and bleb morphology were assessed in each eye at regular intervals after surgery. At 4 weeks after surgery, anterior chamber radiography was performed to visualize the filtering pathway and bleb function. Finally, we determined the distribution of scar tissue by histopathologic analysis of the eyes after sacrificing the rabbits. These outcomes were observed and compared among the groups using appropriate statistical methods.

**Materials and Methods**

**Materials**

We obtained PLGA (LA/GA = 50/50, Mn = 100,000) from Ji’nan Daigang Biomaterial Co., Ltd. (Ji’nan, China). We purchased CsA (99% purity) from J&K Scientific Ltd. (Sunnyvale, CA, USA). Liquid medical-grade silicone (MED-4244) was purchased from Nusil Silicone Technology (Carpinteria, CA, USA). Medical-grade silicone tubes were purchased from Guangzhou Tianling Silicone Co., Ltd. (Guangzhou, China). All other chemicals were of analytical grade and were used without further purification. Other reagents and drugs included: ketamine hydrochloride (Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China); xylazine (Sangon Biological Engineering Ltd., Shanghai, China); ofloxacin eye ointment (Shenyang Sinqi Pharmaceutical Co., Ltd., Shenyang, China); oxybuprocaine hydrochloride eye drops (Santen Pharmaceutical Co., Ltd., Shanghai, China); and hematoxylin and eosin kits (H&E; Baso Diagnostics, Inc., Zhuhai, China).

**Preparation and Characterization of the GDDs**

The normal GDDs (Fig. 1a) were prepared as previously described. The grooved GDDs with a radial groove pattern on their surfaces (Fig. 1b) were prepared in a special stainless steel mold using a similar method. The mold contained an elliptical depression and some radial ridges with a major axis of 7.68 mm and a minor axis of 6.24 mm. A medical-grade silicone tube was inserted into the hole of the GDD body and some liquid silicone (as used to prepare the GDDs) was used as a substitute for the silicone tube. The GDD body in solidifying process. The coating of CsA-PLGA was applied to the GDD surface as described in our prior report. Optical microscopy and field emission scanning electron microscopy (FESEM, Ultra 55; Zeiss Germany, Oberkochen, Germany) were performed to observe the surface characteristics of the GDD before and after CsA-PLGA coating.

**Implantation of GDDs Into Rabbit Eyes**

For this study, nine male rabbits weighing ~1.5 kg were housed in the animal experiment center for ≥3 days before surgery to familiarize them with the environment. The 18 eyes were divided into three groups and implanted with a normal GDD (GDD group); an uncoated G-GDD (G-GDD group); or a G-GDD coated with CsA-PLGA (CsA@G-GDD group). After anesthetization with ketamine hydrochloride (40 mg/kg body weight) and xylazine (10 mg/kg body weight), a 5-mm parallel incision was made on the conjunctiva at 2 mm from the scleral edge. The conjunctiva was bluntly separated from the sclera. Then, the relevant GDD was fixed onto the sclera with 10-0 silk and a scleral tunnel was made with a 25-gauge needle. Sodium hyaluronate (Shanghai Qisheng Biological Agents Co., Ltd., Shanghai, China) was injected into the anterior chamber from the scleral tunnel to maintain the height of anterior chamber and the GDD tube was inserted into the prepared tunnel. Finally, the incision was closed and tobramycin and dexamethasone ointment (TobraDex; Alcon Laboratories, Inc., Fort Worth, TX, USA) were applied onto each eye twice daily for 2 weeks after surgery to reduce inflammation. One experienced ophthalmologist (XY) performed all surgeries.

**Follow-Up Assessments**

Follow-up assessments were made every 5 days for the first month, every 7 days in the second month, and every 14 days in the third month after surgery. At these time-points, the eyes were observed under a slit lamp to evaluate the anterior chamber and the blebs, and IOP was measured using a rebound tonometer (iCARE Tonovet; iCare, Vanda, Finland). The blebs were photographed using slit lamps and analyzed by the same observer. The bleb survival time of each eye was recorded from the first appearance of a flat, scarred, vascularized bleb.
IOP and bleb survival time were compared using 2-way repeated-measures ANOVA and Bonferroni or Dunnett’s T3 post hoc tests for multiple comparisons to assess the significant differences between groups. Values of $P < 0.05$ were considered statistically significant.

Possible complications and bleb morphology were also monitored during the follow-up period. Bleb morphology was quantified using the Indiana Bleb Appearance Grading Scale (IBAGS), and the mean values were calculated for each group at each time-point. The bleb grading scale focused on four features: height, edge, vascularity, and leakage. Bleb height was determined relative to the cornea thickness (CT) as H0 (flat blebs); H1 (0–1 CT); H2 (1–2 CT); and H3 (>2 CT). For edge, the range of the blebs was measured relative to the hour range on a clock face: E0 (<1 hour); E1 (1–2 hours); E2 (2–4 hours); and E3 (>4 hours). Vascularization was defined as classified as V0 (pale blebs); V1 (no vascularization); V2 (slight vascularization); V3 (moderate vascularization); and V4 (severe vascularization). Leakage was classified as L0 (no leakage); L1 (passive leakage); and L2 (active leakage). We compared the IBAGS scores using 2-way repeated-measures ANOVA. Dunnett’s T3 post hoc tests were used for multiple comparisons to assess the significant differences between groups. Values of $P < 0.05$ were considered statistically significant.

**Anterior Chamber Radiography**

Anterior chamber radiography was performed 4 weeks after surgery. Before anterior chamber radiography, eyes were injected with 100 µL of 1% sodium fluorescein solution (Alcon Laboratories, Inc.) to visualize whether the filtration channels were open or closed. The number of open pathways in each group was compared using $\chi^2$ tests. We also assessed the area of fluorescein diffusion and compared it with the bleb range to assess whether the filtration pathway was partly or completely open according to whether the diffusion area was smaller than or equal to the bleb range. The procedure was recorded with a camera (CANON EOS 60D; Canon, Inc., Tokyo, Japan) and slit lamp illumination. Images were recorded for 60 seconds per procedure. The drainage time was recorded from the time when fluorescein reached the inner orifice until it diffused to the largest area. If fluorescein did not enter the drainage tube, the drainage time was recorded as 60 seconds (i.e., the maximum recording time). We also observed the largest area of fluorescein diffusion in each filtrating bleb and calculated the relative area compared with the area of the GDD body. Results were compared using 2-way ANOVA with Bonferroni or Dunnett’s T3 post hoc tests for multiple comparisons to assess the significance of differences among groups. Values of $P < 0.05$ were considered as statistically significant.

**Histology**

All rabbits were sacrificed at 12 weeks after surgery by injecting air into the auricular veins. The eyes in each group were removed and fixed in 4% paraformaldehyde for histologic tests. A rectangular box with cross-sectional dimensions of 2 × 2 cm that contained the filter bleb and all surrounding tissues, corresponding to the black dashed frame in Figure 1c, was dissected from each eye. The rectangular box included the whole bleb and the whole layer of the wall of the eyeball under the bleb and part of the cornea. The tissue samples were stained with H&E and observed under a microscope. Photographs of the tissues were obtained using a camera (Canon, Inc.) and slit lamp. The photographs of each bleb were merged using image editing software (Photoshop CC, version 14.0; Adobe, Mountain View, CA, USA). The bleb morphology was evaluated qualitatively and the area of scar tissue in each slide was calculated using ImageJ software (http://image.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA).

**RESULTS**

**Characterization of the GDDs**

Sample photographs of normal GDD and G-GDD are shown in Figures 2a and 2b. The FESEM images showing the surface morphology of the G-GDD and the CsA@G-GDD are shown in Figures 2c and 2d.

As shown in Figure 2c, the surface of the G-GDD was quite smooth, except for a few scratches caused by the rough surface of the stainless steel mold. The surface of the CsA@G-GDD was characterized by a meshwork structure with a mean pore area of $0.30 \pm 0.03 \mu m^2$ and a mean pore density of $24.72\% \pm 2.89\%$ (Fig. 2d). The mean thickness of the CsA-PLGA coating was $7.03 \pm 0.29 \mu m$, as measured from the FESEM image of the GDD cross-section (Fig. 2e).
Intraocular Pressure

As shown in Figure 3, IOP decreased sharply after surgery to ~7 mm Hg in all three groups, and there were no significant differences in IOP among the three groups up to 5 days after surgery. At 10 days after surgery, repeated-measures analysis revealed significant differences in IOP among the 3 groups, and the post hoc tests showed that IOP was significantly lower in the G-GDD and CsA@G-GDD groups than in the GDD group (both, $P < 0.001$). These differences were maintained from day 20 onwards. However, IOP was not significantly different between the G-GDD and CsA@G-GDD groups at day 10 ($P = 0.089$) or at any time thereafter. The baseline IOP before surgery was 14.5 ± 0.8 mm Hg, which was similar to the value in our previous report (14.4 ± 0.8 mm Hg).20

Bleb Morphology

We took photographs of the blebs under anterior chamber radiography and slit lamp illumination. The morphology of blebs was assessed in terms of whether they were diffused or localized, and uplifted or flat. The morphologic features provide an indication of bleb function. We also determined the bleb survival time in each eye according to bleb morphology. Figure 4 shows the distribution of bleb survival time in each group. The bleb survival time was significantly longer in the CsA@G-GDD group than in the GDD group.

As shown in Figure 5, the blebs increased in height and enlarged quickly after surgery, and vascularization occurred rapidly. Within the first 10 days after surgery, there were no apparent differences in bleb morphology among the three groups. However, after day 10, the blebs became flattened, the edges of the blebs shrank, and the extent of vascularization decreased gradually.

As shown in Figure 6, five days after surgery, the blebs in all three groups had increased to their maximum height and then gradually flattened with time. The blebs in the CsA@G-GDD group were taller than those in the GDD group, and the difference in height was statistically significant on day 10 ($P = 0.003$). There were no significant differences in the areas of blebs among the 3 groups, until 20 days after surgery. On day

![Figure 4: Box and whisker plot of bleb survival time. *P < 0.001 for the CsA@G-GDD group compared with the GDD group.](image)

![Figure 5: Photographs of bleb morphology. The columns show the changes in morphologic features of a single eye in each group over time. Each row compares the morphologic features between individual eyes from each group at the same time. The black arrowheads show the range of blebs. Because there were negligible changes in bleb morphology beyond 35 days after surgery, only photographs obtained up to day 35 are shown.](image)
lower in both G-GDD groups than in the GDD group, although the drainage time tended to be greater in the CsA@G-GDD group. The diffusion area was significantly greater (i.e., better) in the CsA@G-GDD group than in the GDD group and the G-GDD group.

**Histology**

Twelve weeks after surgery, the rabbits were killed and their eyes were processed for H&E staining to evaluate the morphology of the surgical field (Fig. 9). Because it was difficult to stick the silicone GDD bodies and tubes to the slides, the blebs on the slides were empty. The scar tissue of blebs in the G-GDD group was less extensive than in the GDD group, and was less extensive in the CsA@G-GDD group than in the G-GDD group. In >50% of eyes, the blebs in the GDD and G-GDD groups were divided into two regions by a layer of fibrous scar tissue. This phenomenon did not occur in any eye in the CsA@G-GDD group.

**DISCUSSION**

Scar formation is a physiologic reaction to wounds that are intended to maintain the barrier to the external environment. However, scar tissue may block the filtrating pathways in eyes and ultimately lead to failure of filtration surgery. The histologic features of scar tissue formation include enhanced fibroblast proliferation, synthesis and secretion of collagen, and deposition of extracellular matrix. Therefore, the inhibition of fibroblasts in the surgical field may attenuate scar tissue formation. Cyclosporin A suppresses collagen expression in fibroblasts. Our earlier study also demonstrated that CsA reduces fibroblast viability in a dose- and time-dependent manner, and that the concentration 4 μg/mL appears to be optimal in terms of inhibiting scar formation with the fewest side effects. These results may explain how the CsA delivery layer improved the outcomes of GDD implantation.

Implantation of GDD is now believed to be an effective method for treating refractory glaucoma, and has a lower failure rate than trabeculectomy in the tube versus trabeculectomy study. These benefits are related to the large GDD body, less disturbance of the anterior chamber, and greater distance from the anterior conjunctiva where scar formation is more active because Tenon’s membrane is thicker in this region. However, GDD implantation is sometimes associated with complications, such as hypotony with suprachoroidal hemorrhage and shallowing of the anterior chamber, tube obstruction by fibrin clot, and long-term failure caused by bleb fibrosis. Antimetabolic drugs reduce fibrosis and scar formation, but may contribute to bleb leakage. Accordingly, it is believed that antimetabolic drugs should be delivered at lower concentrations and for longer times.

In our prior report, and as reported for the GDD group in the present study, anterior chamber radiography at 4 weeks after surgery showed that fluorescein staining was limited to the outer orifice of the silicone tube and to the connection between the silicone tube and the GDD body in some cases. Meanwhile, H&E staining of tissue samples taken 12 weeks after surgery (see Fig. 9) revealed that the thickest part of the scar tissue coincided with the location of the outer orifice of the silicone tube. In our prior study, because anterior chamber radiography revealed limited fluorescein staining in one eye, we performed dissection to determine the structure of the blebs (see Fig. 10). During dissection, as soon as we excised the scar tissue, yellow fluid (aqueous humor with fluorescein) flowed out immediately and the IOP decreased, which meant the pathway was open but the bleb was unable to absorb the aqueous humor. Therefore, we hypothesized that radiated grooves on the GDD body would improve the drainage of...
aqueous humor from a wider area of the conjunctiva, thereby reducing the extent of fibrosis. To our knowledge, no studies have made a similar modification to GDDs. To test this hypothesis, we implanted the G-GDDs into rabbit eyes and assessed whether this design improved drainage and inhibited scar formation. Our results indicate that the G-GDDs were associated with better drainage than the ungrooved GDDs.

In 2010, Abbott Medical Optics published a patent for a novel glaucoma shunt that had selective cell adhesion regions, with increased propensity for cell adhesion and smooth surface regions with relatively lower propensity for cell adhesion. The proposed shunt had a structure resembling leaf veins with interconnected channels for fluid flow that isolated the cell adhesion regions from each other. A similar effect may occur with our novel G-GDDs. The main difference between their shunt and our G-GDD is that we directly molded grooves onto the plate rather than guiding cells to form channels.

Our rabbit model of GDD implantation simulated GDD implantation in human eyes, and the postsurgical manifestations were similar. The blebs rose immediately after completing surgery and slowly flattened, while the IOP decreased by about 50% after surgery and then gradually increased to a plateau. We found some differences in IOP among the three groups during the follow-up period. In particular, the IOP at 12 weeks in the GDD group was higher than in the other groups, and was even higher than the initial level in this group. The elevated IOP in the GDD group possibly contributed to the postsurgical inflammatory state. The IOP at 12 weeks was similar between the G-GDD and CsA@G-GDD groups, and was about 2 to 3 mm Hg lower in these groups than in the GDD group. However, the time taken for IOP to reach the plateau differed among the

FIGURE 7. Anterior chamber radiography. Representative images obtained during anterior chamber radiography at 4 weeks after surgery of all 24 eyes. Images are shown at the time at which fluorescein had diffused to the maximum area. Eyes in each group are shown in the same column. The red arrowheads show the range of the blebs and the blue arrows show the drainage tube.

FIGURE 8. Anterior chamber radiographic parameters. (a) Status of pathways in each group. (b) Mean ± standard error drainage time. (c) Mean ± standard error diffusion area. *P < 0.05 for the indicated comparisons.
In clinical practice, a stable filtrating pathway is usually established within 3 months after surgery, and the establishment of functional blebs is a critical factor for controlling IOP. Sacu et al. and Klink et al. suggested that the morphology of blebs in the early stage was significantly associated with postsurgical IOP and prognosis. By using the IBAGS classification, we could evaluate the morphology of the blebs in a semiquantitative manner. This system was proposed by Cantor et al. in 2003. Before the introduction of the IBAGS classification, Kronfeld and Migdal and Hitchings classified blebs in clinical settings under slit lamp illumination, but they did not assess all of the morphologic features of blebs. Now, the IBAGS classification and the Moorfields bleb grading system (MBGS) are widely used to evaluate and classify the morphology of posttrabeculectomy blebs under slit lamp illumination. There is no specialized grading scale designed for use after GDD implantation. Because the IBAGS is considered to be easier to use than the MBGS while they perform adequately for most bleb grading parameters, we used the IBAGS in this study.

In this study, the blebs in the CsA@G-GDD group were higher and covered a larger range than in the GDD group. By contrast, bleb vascularization was not significantly different among the three groups, which indicates that CsA and the presence of grooves do not influence vascularization. The morphologic results imply that the drug delivery system on GDDs had a significant effect on maintaining the height of blebs, but the presence of grooves did not. Nevertheless, the design of the GDD did influence the range of the blebs, because the area covered at least 2 hours on a clock face in both G-GDD groups. However, we could only use the IBAGS classification to judge the range of blebs to a smallest size of 2 hours, which reduced the accuracy of this scale. Regarding bleb height, we measured the width between the conjunctiva and the GDD body instead of the sclera in the IBAGS, which might introduce some bias.

Anterior chamber radiography showed that the blebs in four of six eyes in the GDD group lacked drainage function at 4 weeks after surgery, whereas all of the eyes in the other groups showed intact drainage function at this time. All of the filtration pathways in eyes in the G-GDD group were partly open, while most pathways in eyes in the CsA@G-GDD group were completely open. Anterior chamber radiography can depict whether the filtrating pathway is open or blocked. In some blebs in the CsA@G-GDD group, vessels (lymphatic vessels or veins) contained fluorescein, confirming drainage from the blebs (Fig. 11). This phenomenon was not seen in the other two groups. Considering these findings, we think that the activity of the lymphatic or venous drainage system in the CsA@G-GDD group was stimulated by CsA, but this possibility requires further investigation.

By comparing the H&E-stained slides, we can conclude that each group has distinct features. In the GDD and G-GDD groups, the blebs in >50% slides were separated into two parts by a layer of fibroblasts. We think that the layers of fibroblasts formed after the GDDs were covered by scar tissue and the aqueous humor passed outside rather than inside the tube, creating another subconjunctival vesicle. These new vesicles also developed scar tissue. A similar structure was also reported by Wells et al., who believed that “cystic blebs” were associated with a ring of scar tissue around the GDD body. When we examined the scar tissue layer, we found that the scar tissue was thickest around the junction between the tube and body of the GDD (blue arrows in Fig. 9). The irregular shape and fluid dynamics probably caused greater fibroblast proliferation, resulting in a thicker scar layer. Moreover, we found that scar tissue layer was thicker in the GDD group than in G-GDD groups. We think that the groove facilitates the drainage of aqueous humor from a larger region, improved the fluid dynamics, and helped the aqueous humor to break any blockage formed by scar tissue. The height and range of blebs were significantly greater in the CsA@G-GDD group than in the GDD and G-GDD groups, which might be related to a contractile effect of the scar tissue in the GDD and G-GDD groups.

Taken together, these findings indicate that implantation of an uncoated or CsA-PLGA-coated G-DD reduced the IOP at 3 months after surgery compared with implantation of an ungrooved GDD. In addition, bleb survival time, bleb height, and bleb range, and diffusion area were significantly greater in the CsA@G-GDD group than in the GDD group. Based on these findings, we propose a hypothesis to explain how the novel GDDs attenuated scar tissue formation. First, the continuous delivery of CsA from the PLGA layer inhibited the growth of
fibroblasts and increased the activity of lymphatic vessels or veins, which needed further study. In addition, the grooves maintained the flow of aqueous humor, and prevented the scar tissue from completely blocking the filtrating pathway. Although the G-GDDs did not affect change the morphology of blebs, they significantly improved the filtration function of blebs. Accordingly, creating grooves in the GDD and coating the GDD with a layer of CsA-PLGA yielded a GDD capable of maintaining a large area of functional blebs.

A limitation of our study is that we did not determine CsA distribution in vivo because local disturbance could interfere with the surgical outcome. Therefore, we could not analyze the release rate, pharmacokinetics, or penetration of CsA in vivo. Such data are needed to provide direct evidence that the efficacy of the CsA@G-GDDs was driven by the release of CsA. Such data will also be useful to explore how the novel GDDs worked in vivo.

Before these novel GDDs can be implanted into patients, we should consider that the extent of scar tissue formation differs markedly among individuals, so the need for antimetabolite drugs varies between patients. It is also important to consider that inadequate doses of antimetabolic drug are associated with very low success rates, while excessive doses may cause complications (particularly leaks, which increase the risk of adverse effects such as infection, scleromalacia, and scleritis). Therefore, the concentration and duration of administration of anti-metabolic drugs may need to be personalized for individual patients to improve the outcomes of glaucoma surgery. Personalized medicine might be set according to the thickness of Tenon’s capsule, the degree of tissue vascularity and bleeding, and possibly, different receptor responses to drugs. The novel GDDs might allow us to conveniently adjust the dose of the antimetabolic drug to achieve personalized drug delivery.

CONCLUSIONS
We investigated the functional outcome of filtration surgery by implanting improved GDDs with surface grooves and a composite coating of CsA and PLGA in experimental rabbit
eyes. Compared with the normal GDDs, the CsA@G-GDDs inhibited postsurgical scar formation and improved the surgery success rate. In addition, the presence of a CsA-PLGA coating was associated with significant improvements in bleb survival time, bleb morphology, and bleb function (as assessed by anterior chamber radiography). Histologic analysis also revealed that implantation of G-GDDs and CsA@G-GDD was associated with fewer scars compared with the control GDDs, although the underlying mechanism is unclear. Therefore, while we have provided preliminary data supporting the safety and feasibility of these implants for treating glaucoma, further research and improvements to their design may be required before they could be tested in patients.

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