Animal Models of Proliferative Vitreoretinopathy and Their Use in Pharmaceutical Investigations

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Keywords

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Abstract

Animal models are indispensable for pharmaceutical investigations. However, investigators often have difficulty choosing the appropriate model for their research. To provide a comprehensive and convenient source of information about animal models of proliferative vitreoretinopathy (PVR), the current review sorted and analyzed representative animal models for pharmacotherapy of PVR since 1976.

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Introduction

Proliferative vitreoretinopathy (PVR) is not a stand-alone disease, but it is considered the endpoint of a number of intraocular diseases. It is characterized by the formation of contractile membranes within the vitreous and along the preretinal and subretinal surfaces [1]. In spite of gradual improvements in surgical success rates over the past decades, PVR remains a major barrier to success-

ful repair of retinal detachments (RD), with an incidence of 5–11% [2]. Moreover, it is implicated in over 75% of postsurgical redetachments [2, 3]. Multiple strategies, including surgery, have been developed to inhibit this disease process. PVR surgery can be challenging, even for experienced vitreoretinal surgeons, and anatomic success does not necessarily lead to functional improvement [2]. Adjunctive pharmacotherapy, with new molecules and delivery systems, offers promise for improved outcomes [3]. Animal models have an essential role in screening of various drugs [4]. For more than 40 years, lots of scientists and doctors have conducted relevant research. Landmark models, including a classic cell intravitreal injection model, introduction of blood components, surgical manipulation, and so forth, have been developed continuously. This review will focus on animal models used for drug screening and discuss their properties and limitations.

Adjunctive Therapeutics for PVR

Pharmacological adjuncts to surgical management of PVR usually target its cellular components and pathological processes [5]. Multiple medical treatments have been used to prevent inflammation (the first phase of PVR) and

inhibit cell proliferation (the second phase) [1]. Tested medical agents include: (1) corticosteroids and other anti-inflammatory agents [6–8]; (2) 5-fluorouracil, vincristine, doxorubicin, cisplatin, dactinomycin, bleomycin sulfate, etoposide, mitomycin, cytarabine, daunorubicin, adriamycin, 2'-benzoyloxycinnamaldehyde [9–11], methotrexate [12, 13], and other antineoplastic drugs to prevent the proliferative response of PVR; (3) retinoic acid [14], matrix metalloproteinase inhibitors [15], and other agents with specific antiproliferative targets; (4) compounds that specifically target growth factors or their pathways, such as hypericin (an inhibitor of the protein kinase C pathway [16]); herbimycin A [17] and dasatinib (tyrosine kinase inhibitors) [18]; tranilast (a potent inhibitor of transforming growth factor [TGF]- β [19]), LY-364947 (a TGF- β receptor 1 inhibitor [20]); taxol (a drug that stabilizes microtubules and may therefore inhibit cell contractility [21]); colchicine (inhibits the formation of microtubules as well as inhibiting fibroblast proliferation [22]) and suramin (an antiparasitic agent that interferes with growth factor binding [23]); and (5) other bioactive factors or compounds like octreotide [24] and resveratrol [25].

Combination therapies, which consist of 2 or more compounds targeting different steps in the proliferative and inflammatory responses that trigger PVR, have also been employed with the intent of obtain synergistic inhibition [2]. Different combinations of retinoic acid, retinol, daunorubicin, triamcinolone, and carmustine have been shown to be effective in PVR models [6, 26–28].

Although injection or perfusion of free drug into either the vitreous chamber or the subconjunctival space has proven effective in reducing the PVR incidence in humans as well as in animal models [29], a major limitation to the successful treatment of PVR using pharmacological adjuncts is the difficulty in achieving therapeutic drug levels in the microenvironment of the retinal surfaces over a sufficiently long period to adequately inhibit membrane formation. Single intravitreal injections of therapeutic agents have a relatively short half-life, which can be further shortened by vitrectomy, aphakia, and postoperative inflammation [9]. Therefore, sustained drug delivery systems, such as biodegradable polymers [10, 30], silicone oil [26], and porous silicon [31], are being investigated [2].

In spite of considerable efforts to identify effective and safe adjunctive therapies, clinical success is still rare. This could be in part due to the lack of knowledge of the pharmacokinetics of these drugs when they are utilized for PVR prevention [1]. Therefore, comprehensive evaluation and investigation of any drug candidate in experimental models is essential.

Design of PVR Animal Models for Pharmaceutical Investigation

A comprehensive understanding of the pathobiology of PVR may eventually allow the development of targeted medical prophylaxis and/or adjunctive therapies. Experimental models of PVR that mimic human disease and can also be used for drug screening are needed.

PVR progresses in a predictable timeline [32] reminiscent of an anomalous wound-healing process. There is an initial inflammatory phase, a secondary proliferative response, and modulation of the scar which causes contraction [14, 33]. The breakdown of the blood-ocular barrier caused by a retinal break that enables effusion of inflammatory cells (macrophages, leukocytes, and platelets) which release growth factors, including platelet-derived growth factor, TGF- β , and epidermal growth factor [34, 35]. Retinal breaks expose glial cells, retinal pigment epithelium (RPE), and other cells, triggering an exuberant healing process that is amplified by the intense inflammation. Upon loss of contact with the overlying retina, proliferation occurs as a rapid response with the involvement of RPE, glial cells (including Müller cells, astrocytes, and microglial cells), pericytes, endothelial cells, and macrophages [36, 37]. Some of these cells transform into myofibroblasts and fibroblasts. Ultimately, vitreous, epiretinal, and subretinal membranes form. After a period of 8–10 weeks, these membranes often contract, placing tangential traction on the retina. The traction can pull the delicate retinal tissue into fixed folds that detach the photoreceptors from the underlying RPE [2]. If not relieved by surgical intervention, the traction can progress and result in stretch tears and subsequent rhegmatogenous detachments [38].

Several key factors in this process have been elucidated and have become the basis for the design of animal models for drug screening (Table 1). A number of cells, including RPE, leukocytes, macrophage, glial cells, fibroblast-like cells, and others, are implicated in the development of PVR [39]. They not only constitute the proliferative membrane but also serve as a source of growth factors. Therefore, many animal models are designed to introduce exogenous cells into the vitreous cavity. Cell types include autologous or homologous fibroblast cells including dermal [40, 41], conjunctival [16, 19], corneal [42] and choroidal fibroblast [21], autologous, homologous or heterologous RPE cells [43–45], and activated macrophages [39, 46]. Evidence suggests that the primary factor in the development of traction RD and membrane formation are platelet-derived factors [1]. Therefore, in-

Table 1. Design of proliferative vitreoretinopathy animal models

Design	Rationale
Cell intravitreal injection	Introduction of cell composition of proliferation and resource of growth factor
PRP or blood intravitreal injection	Introduction of platelet-derived factors
Artificial retinal break and blood-ocular barrier breakdown	Exposure of blood/retina-derived cells and factors
Intravitreal injection or transgenic expression growth factors/cytokines	Introduction of the necessary factors for PVR development
Artificial vitreous disturbance	Disruption of the PVR inhibitory properties of normal vitreous
Artificial chronic RD	Mimicry of advanced PVR

PRP, platelet rich plasma; PVR, proliferative vitreoretinopathy; RD, retinal detachment.

jection of blood products is often used to supplement injection of cells or surgeries [45, 47–50].

Retinal break is considered the critical factor that triggers the onset of PVR by exposing RPE cells to vitreous [51]. Several studies have identified clinical characteristics that are associated with the development of PVR, such as extensive or multiple retinal tears, vitreous hemorrhage, and multiple previous surgeries, all of which suggest a breakdown of the blood-ocular barrier that allows serum factors and cells to enter the eye [1, 52]. PVR likely occurs as a result of interactions between cells derived from blood, and factors that enter the eye after the retinal tear [2]. Surgical manipulation, like retinotomy, cryopexy [53–55], dispase injection [4, 56, 57], and scleral injury, can be performed to mimic retinal damage and blood-ocular barrier breakdown [58, 59].

For PVR development, some factors must be present to transform the healing mechanism into an exaggerated response and produce hyperplastic growth of fibrotic tissue [1]. In addition, various cytokines appear to mediate the proliferative response [14]. Numerous growth factors and cytokines have been demonstrated as being involved in this process. Intravitreal injection or transgenic expression using a viral vector has been used to introduce growth factor or cytokines into eyes [60, 61].

Another factor related to the pathogenesis of PVR is the status of the vitreous. Physicochemical properties of normal vitreous prevent membrane formation [62, 63], and inhibitory factors that prevent the proliferation of endothelial cells, myofibrillar cells, and fibroblasts have been identified in normal vitreous [64]. Therefore, alteration of the normal vitreous properties appears to be a necessary requirement for the development of PVR. In animal PVR models, gas compression and vitrectomy are 2 main methods to disturb the vitreous, usually before in-

travitreal injection or other surgical manipulations [49, 65–68]. A direct way to mimic advanced PVR is the development of chronic RD simply by subretinal injection [69, 70]. This model develops some features of PVR, including activation of the Müller glia and extension of glial processes below the external limiting membrane [69].

Application of PVR Models for Pharmaceutical Investigation

In vitro

RPE cells and fibroblasts, important cell types involved in PVR pathogenesis [5, 71, 72], and human PVR membrane-derived primary cultures [73] are commonly used as in vitro models. Several specific antiproliferative, anti-inflammatory agents, including methotrexate [73], interleukin-4 [74], immunotoxins [75, 76], interferon- γ [77], 5-fluorouracil, daunorubicin and others [78], are being investigated in these models. An obvious advantage of employing cells for drug screening is their practicability and controllability. However, the sensitivity of different cell types to certain drugs may be quite varied [78], and this variability may lead to difficulty with evaluation of drug efficiency.

In vivo

The earliest developed models of PVR often injected dermal fibroblasts to initiate PVR. Afterwards, other cell types, such as corneal, choroidal, and conjunctival fibroblasts, RPE cells, and macrophages, were introduced for PVR stimulation. These cell injection models are widely used. The significant advantage of a simple cell injection model is minimal invasion. In addition, certain growth factors and platelets can be injected simultaneously to en-

hance the PVR-induced effect [25, 79]. PVR features typically develop commensurate to the amount of cells injected and also relate to the injection medium [80]. In addition to the injection of different types of cells, other manipulations (such as platelet rich plasma/blood injection and surgical manipulation) are often used as they can be synergistic.

Artificial trauma, including scleral incision and other surgical manipulations, is also used to develop PVR models. Briefly, a standard 8-mm circumferential scleral incision is made through the pars plana avoiding the lens and retina. The prolapsed vitreous is resected and the wound repaired with 8–0 sutures, followed by injection of autologous blood or ferrous iron [47, 81, 82]. Some models involve multiple surgical manipulations (e.g., gas compression, vitrectomy, cryotherapy, and retinotomy). Different combinations of cells or factors also can be injected along with these surgical manipulations to stimulate PVR. Recently, a chronic RD murine model was developed by subretinal injection to mimic the advanced stage of PVR [69, 70]. One thing should be kept in mind when artificial trauma is involved in model establishment: the PVR that occurs after penetrating trauma differs from PVR following RD surgery in many aspects. Therefore, model selection should be based on the targets of the specific drug tested.

Commonly used animal models are summarized in Table 2. Models with slight modifications based on other representative models resulting in inconspicuous model property changes were not included (i.e., gas compression replaced by hyaluronic acid compression). The publishing time of the earliest literature that the author could find in public literature resources using the key words of this review is shown as “establishment year,” and RD is taken as the main clinical landmark.

Different animal species have their intrinsic pros and cons. Rabbit models have been widely used. Their large vitreous volume and the ease of manipulation with less risk of damage to the lens/retina are advantageous. However, rabbits’ retinal structure including blood vessels and nerve fiber distribution is different from that of humans, resulting in limitations for pathologic and immunohistochemical examinations. In contrast, rodent models are less commonly employed. Although genetically modified murine species are widely available, their large lens size and small vitreous volume affect the feasibility of manipulation (e.g., intravitreal injection) and fundus examinations [39, 83]. Pig models are rarely used; however, their eyes are similar in size to the human eye and this facilitates surgical manipulation. Moreover, their retina is holangiotic and they also have a cone-enriched area centralis which is similar to the human fovea [55, 84].

Classification of Animal PVR in Pharmaceutical Investigations

Fastenberg’s classification is a commonly used classification of intact vitreous PVR models based on the clinical stages of PVR development, in which 5 stages are defined as follows [80]:

- stage 1: intravitreal membrane
- stage 2: focal traction, localized vascular changes, hyperemia, engorgement, dilatation, and blood vessel elevation
- stage 3: localized detachment of the medullary ray
- stage 4: extensive RD, total medullary ray detachment, and peripapillary RD
- stage 5: total RD, retinal folds, and holes

The following classification involving earlier stages was proposed for a vitreous compressed model [66] and simple cell intravitreal injection model [85]. Because of its fine scale, this grading system is particularly useful for quantifying pharmacologic effects:

- stage 0: normal retina. The retina looks normal at this stage. Occasionally, fine intravitreal strands are seen extending from the injection site to the posterior retina.
- stage 1: surface wrinkling. The retina shows an irregular surface of the medullary wings or visual streaks with a beaten metal appearance.
- stage 2: mild pucker. Single or multiple small focal contractions resulting in a slight displacement of vessels toward the center are observed. These do not involve all of the medullary wing(s) and are not elevated. In rare cases, these lesions may cease development at this stage and disappear at a later time.
- stage 3: severe pucker. The preretinal contraction involves the whole area of the wing(s) and may consist of a single pucker or multiple puckers. The retina may be tented up but not by vitreous strands.
- stage 4: elevated pucker. At this stage, antero-posterior traction is observed, with the pucker(s) becoming elevated by vitreous strands.
- stage 5: partial RD. Detachment of the medullary wing occurs but involves only one wing. RD is seen with or without vitreous strands.
- stage 6: low detachment. RD involves both medullary wings, but the remainder of the avascular retina is attached.
- stage 7: total detachment. RD is seen over most of the avascular retina, usually with the appearance of a closed funnel detachment. In most cases retinal holes are visible. Sometimes unequivocal neovascularization appears from the disc or cryotherapy site.

Table 2. In vivo models for pharmaceutical investigation

Model	Establishment year	Animals	Clinical landmark		Concise common procedure	Representative tested therapeutic agents
			first time point of RD being noticed	percentage of RD at the end of follow-up		
Autologous dermal fibroblast cell injection [40, 96]	1976	Rabbit	1×10 ⁶ cells, 11–30 days; 3×10 ⁶ cells, 4 days	4 weeks: 1×10 ⁶ cells, 56%; 3×10 ⁶ cells, 100%	Injection of fibroblast cells into intact eyes	Triamcinolone [7], suramin [23], and methotrexate [97]
Artificial trauma [15, 47, 81, 82, 86]	1979	Rabbit	12 days	6 weeks: 0.4 mL blood, 78–82%; 0.2 mL blood, 43%; 0.1 mL blood, 0%; 200 µg elemental iron, 100%; 100 µg elemental iron, 100%; 50 µg elemental iron, 0%	Vitrectomy, autologous blood/ferrous iron injection	Naproxen and 5-FU codrug, prinomastat [15], and pifrenidone [98]
Homologous dermal/corneal/choroidal/conjunctival fibroblast injection [99, 100]	1982	Rabbit	7×10 ⁵ cells, 1 day; 2.5×10 ⁵ cells, 1 day	4 weeks: 2.5×10 ⁵ cells, 25–90%; 5 weeks: 7×10 ⁵ cells, ~60%	Injection of fibroblasts into intact eyes	Hypericin [16], herbimycin [17], taxol [21, 42], and tranilast [19]
Homologous RPE cell injection [44]	1982	Rabbit	2 weeks	4 weeks: 100%	Injection of RPE cells into intact eyes	Disintegrins [88] and DNR [101]
Homologous dermal fibroblast injection + vitrectomy [41]	1983	Rabbit	Without silicone oil, 14 days	4 weeks: without silicon oil, 100%; with silicon oil, 50%	Transcleral cryopexy; after 2 weeks, vitrectomy; after 2 weeks, fibroblast injection	Taxol [42]
Gas compression + homologous fibroblast injection [66, 67, 102]	1986	Rabbit	25,000 cells, 4 days; 50,000 cells, 2 days; 100,000 cells, 7 days	4 weeks: 25,000 cells, 88–91%; 50,000 cells, 100%; 100,000 cells, 50%	Perfluoropropane or sulfur hexafluoride gas injection; after 7–10 days, fibroblast cell injection	Retinoic acid [30], retinoic acid [26], and carmustine [27]
Activated macrophages [46, 103]	1987	Rabbit	2 weeks	6–9 weeks, 38% RD	Injection of 8×10 ⁵ homologous macrophages into intact eyes	Triamcinolone [6] and a combination of DNR and triamcinolone [28]
Heterologous RPE cell injection [104–106]	1987	Rabbit	7 days	4 weeks, 75%	Injection of human, bovine, or rat RPE cells into intact eyes	5-FU [105]
Multiple surgical manipulations [107]	1991	Rabbit	N/A	4–12 weeks, PVR developed in 90% of eyes	Pars plana lensectomy, core vitrectomy, and penetrating retinal endodiathermy	Triamcinolone and 5-FU codrug [108]
Homologous conjunctival fibroblasts injection + PRP [49]	1995	Rabbit	1 day	29 days, 100%	Injection of 1×10 ⁵ conjunctival fibroblasts and PRP (0.1 mL, 75,000 platelets)	DNR encapsulated in liposome [109]
Disperse injection [56, 57, 87]	1998	Rabbit, guinea pig, and mouse	N/A	Overall, with increased doses of disperse, the severity of PVR increased	Injection of a different dose of disperse into the subretinal space or vitreous	Ribozyme [87] and octreotide [24]
Gas compression + homologous RPE injection [11, 110]	2002	Rabbit	7 days	4 weeks, 72.7%	Perfluorocarbon or sulfur hexafluoride gas injection; gas-fluid exchange; 7–10 days later, injection of (1–2) ×10 ⁵ or 5×10 ⁴ RPE cells	2'-benzoyl-oxy-cinnamaldehyde [11], doxorubicin [110], and dexamethasone [3]
Vitrectomy + artificial RD + RPE cells injection [84]	2012	Swine	3 days	14 days, 100%	Pars plana vitrectomy followed by subretinal injection and intravitreal injection of RPE cells	Dasatinib [18]
Homologous RPE cells + PDGF-BB injection [25]	2015	Rabbit	7 days	14 days, 100%	Vitrectomy and injection of 1.5×10 ⁵ RPE cells and 50 ng PDGF-BB in 100 µL PBS	Resveratrol [25]

RPE, retinal pigment epithelium. PRP, platelet-rich plasma; 5-FU, 5-fluorouracil; DNR, daunorubicin; PLGA, poly(lactic-co-glycolic acid); PDGF-BB, BB isoform of platelet-derived growth factor.

In a trauma model, the surgical procedure is usually followed by an intravitreal injection of autologous blood, which precludes a reliable clinical observation. Therefore, in addition to a clinical indirect microscopic examination, a detailed fundus evaluation of the enucleated eye

under a dissecting microscopy is used for PVR grading as follows [86]:

- stage 0: attached without evidence of fibrous ingrowth.
- stage 1: attached with minimal traction elevation confined to the medullary ray. Mild fibrous ingrowth is

present upon scleral depression. Occasionally a “clothesline” type of fold is evident within the posterior ray, but the retina surrounding the ray remains attached.

- stage 2: up to 50% of the retina is detached (moderate tractional elevation), usually directly surrounding the ray. Prominent anteroposterior traction involving the disc and medullary ray is evident. Prominent fibrous ingrowth is present, with faint bands connecting the peripheral ray fibrous mass to the disc or ray. The retinal vessels are dilated without overt neovascularization.
- stage 3: between 50–100% of the retina is detached (severe RD), usually associated with an open funnel configuration. Fibrous ingrowth from the wound is severe, and the peripheral retina and ray are drawn towards the fibrous mass.
- stage 4: 100% of the retina is detached, associated with a closed funnel configuration. Fibrous ingrowth is severe, with obvious dragging of the retina causing prominent retinal folds.

Besides, there are also grading methods, especially for dispase injection-induced PVR [87], swine models [84], and tractional RD [65, 88].

Limitation of Current Animal Models, Research Needs, and Future Directions

Animal models have an important role in evaluating various pharmacologic therapies for PVR. However, there are important clinical and pathological differences between the models of PVR and human disease, which deserve careful consideration when they are used for drug screening.

Most commonly, PVR animal models have relied on the addition of cells or factors reported to be found in human PVR and often include other manipulations, such as gas compression and vitrectomy. The models in which PVR is stimulated by intravitreal injection of fibroblasts, RPE cells, or macrophages are widely employed for testing of new therapeutic agents. However, these models are flawed because they introduce large numbers of cells. Moreover, they do not take into account the early crucial steps in PVR development, including cellular transformation and proliferation [53, 89, 90]. If the inhibitory effects of any drugs are tested, injected drugs may affect not only the development of PVR but also the injected cells themselves directly. Thus, inactivated and/or dying cells can not induce PVR resulting in welcome results. Among

the cell injection models, fibroblast injection give rise to doubt. Dermal, corneal, or conjunctival fibroblasts are not involved with the pathogenesis of human PVR. In contrast, injection models that utilize cultured RPE cells and macrophages are more relevant to human disease [80]. However, the macrophage injection model does not expose RPE cells, which are thought to have a critical role in the development of human PVR. Further, the lack of trauma associated with retinal surgery in animals implies the possibility of fewer infiltrating leukocytes and their associated cytokines [35, 80].

Blood exposure can influence the pathogenesis of PVR, both in terms of the rapidity of PVR progression and in terms of membrane formation [80]. Human PVR may be associated with intraocular bleeding [80]. Moreover, the introduction of blood hinders the observation of early features of PVR. Another model that implicates severe media opacity (vitreous hemorrhage and cataract) is the dispase injection model, in which the incidence of vitreous hemorrhage and cataracts increases with higher doses [56, 91].

The time course of the disease is an important aspect of the pathobiology of PVR that needs to be addressed to standardize the testing of various pharmaceutical agents [1]. Although there is a variable time course for different models, the progression of PVR in animal models is generally much faster than in humans. The usual development of PVR in the base model starts quite early, when membranes and strands are seen. RD may occur within days and progresses to a full development of PVR in most models in 4 weeks. The time course of membrane formation and RD in cell injection models depends on the source, type, and amount of cells introduced [80]. Also, the injection medium and subsequent blood product injection can influence the results [80]. The rapid disease progression makes complete inhibition of PVR in the animal model a challenge because the PVR can become quite severe quickly before any pharmacological treatment can be effective. Compared to other cell types, PVR development with the macrophage injection model seems slower. The chronic RD model, in contrast, bypasses all early pathologic steps [69, 70]. Thus, use of this model in drug screening is rare. However, this model can still be useful as its fibrosis feature could be an appropriate target for antifibrotic agents. One pitfall in the design of some animal models is a lengthy follow-up interval, which may be too long to observe the earliest pathologic changes [18].

Efforts have been directed toward developing models that more closely resemble the human pathophysiologic

condition, placing more emphasis on the role of intraocular inflammation, wound healing, and the presence of growth factors than the introduction of external cells into the eye [53, 55, 68, 84, 92]. But those models usually involve surgical manipulation with reproducibility, to a large extent, depending on the operative skills of the surgeon. Transgenic models in which overexpression of various growth factors in the photoreceptor cells leads to traction detachment of the retina [93, 94] are not suitable for drug screening, because forced alteration of the cytokine expression profile likely affects the signal transduction system [95] that may be a target of the tested therapeutic agent. Induction of PVR by injection of dispase is likely to stimulate retinal glial cells to migrate toward the subretinal space [95], but it may be complicated by vitreous hemorrhage, haze, and cataract [56, 57, 87].

Considering the limitations of available models, it is clear that new improved models are needed. One aspect of the ideal model is stimulation of the animal retina to produce the regulatory factors of the wound-healing process instead of introduction of exogenous factors from injected cells, virus, or free factors [1]. With these factors, a spontaneous epithelial-mesenchymal transition of cells like RPE and macrophages after RD can be mimicked [39, 95]. Taking reproducibility and ease of establishment of the model into account, less complicated manipulations would be advantageous.

Conclusion

Although the current management of PVR is primarily surgical, there is an ongoing effort with experimental models to discover adjuvant therapies that might inhibit the development of postoperative PVR and lead to better patient outcomes [2]. However, an agent that fully prevents the development of PVR is not yet available. Existing experimental models of PVR all have limitations that limit their relevance for drug screening. Therefore, optimization of experimental models for PVR continues to be a challenge.

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