Pharm Res (2015) 32:3572–3576
DOI 10.1007/s11095-015-1728-9

EXPERT REVIEW

Antibody-Drug Conjugate (ADC) Research in Ophthalmology—a Review

Jie Shen [1,2] • Mayssa Attar [1]

Received: 3 July 2014 / Accepted: 29 May 2015 / Published online: 10 June 2015

ABSTRACT Similar to cancer, many ocular proliferative disorders could be treated with a specific antibody conjugated to a toxin. Active targeting to inhibit epithelial and endothelial cell proliferation in the eye has been tested using antibody-drug conjugates (ADC) both pre-clinically and clinically. Achieving efficacious drug concentrations in the eye, in particular to treat back of the eye disorders is challenging, and the promise of targeted antibody mediated delivery holds great potential. In this review, we describe the research efforts in drug targeting using ADC for the treatment of choroidal neovascularization (CNV), posterior lens capsule opacification, and proliferative vitreoretinopathy. Among these disorders, CNV represents a more active research focus, with more target antigens tested, given the disease prevalence and wider target antigen selection based on current understanding of the pathophysiology of the disease. However, the only research advancing to testing in clinical stage is for posterior lens capsule opacification. Compared to oncology, ADC research and development in ophthalmology is much more limited, possibly due to availability of successful therapies that could be administered locally with limited concern of off-target drug toxicity.

KEYWORDS antibody-drug conjugate · choroidal neovascularization · ocular · posterior lens capsule opacification · proliferative vitreoretinopathy · safety

✉ Jie Shen
shen_jie@allergan.com

[1] Department of Pharmacokinetics, Dynamics and Disposition, Allergan, Irvine, California 92612, USA

[2] Allergan, Inc., 2525 Dupont Drive, Irvine, California 92612, USA

INTRODUCTION

Antibody-drug conjugate (ADC) in general refers to a new class of highly potent biopharmaceutical drugs designed as a targeted therapy for treatment of cancer and has the advantage over traditional small molecule cancer therapy in decreased off-target toxicity and therefore better clinical safety profile. Moreover, when compared to pure antibody therapies, ADC drugs tend to be more efficacious since they do not rely solely on target modulation to impact tumor growth. As a result, many ADC drugs have been successfully marketed to treat different types of cancer and even more are at various stages of clinical development (1). In contrast, ADC research and development to treat ocular diseases is much more limited with few examples of candidates advancing to clinical testing. This is most likely due to availability of successful therapies that could be administered locally with limited concern of off-target drug toxicity for many ocular diseases already.

Similar to cancer, however, many ocular proliferative disorders could be treated with specific antibody conjugated to a toxin. Active targeting to inhibit epithelial and endothelial cell proliferation in the eye has been tested using ADC agents both pre-clinically and clinically. Among these disorders, CNV represents a more active research focus given the disease prevalence and wider target antigen selection based on current understanding of the pathophysiology of the disease.

In this review, we describe past research efforts in drug targeting using ADC for treatment of CNV, posterior lens capsule opacification, and proliferative vitreoretinopathy and offer our view on the potential future for this type of therapy for ophthalmology indications.

TREATMENT OF CHOROIDAL NEOVASCULARIZATION

Choroidal neovascularization (CNV) is the growth of abnormal and leaky new blood vessels beneath the retinal pigment epithelium (RPE) and between RPE and the neural retina. This is a common symptom of degenerative age-related macular degeneration (AMD), a leading cause of irreversible blindness among the elderly in developed countries (2). Vision loss occurs when the abnormal growth and leakage of blood vessels happen in the macula, a specialized portion of the retina responsible for the best visual acuity.

To develop ADCs that effectively target CNV, the antibodies need to recognize antigens that are unique to the endothelial cells of the abnormal leaky new vessels. Based on this, potential antigen candidates could be identified based on scientific data suggesting preferential or up-regulated expression in CNV tissues when compared to normal tissues.

Vascular endothelial growth factors (VEGF) are the most well established and proven target for treatment of CNV (3,4). VEGF is the cytokine primarily responsible for blood-vessel growth, and is inhibited when the anti-VEGF drugs are injected intravitreally into the eye. Mayo *et al.* reported conjugation of a photosensitizer verteprofin with antibodies against VEGF (5). Verteporfin (Visudyne) is the only FDA approved photodynamic therapy for ophthalmic use and was conjugated to rabbit antimouse VEGF polyclonal antibodies. VEGF-expressing murine endothelial cells were incubated with the conjugate with and without subsequent laser exposure. The experiment demonstrated that conjugated verteprofin killed cellular targets at least as effectively as verteporfin alone. Since VEGF is a soluble protein target, however, ADC targeting VEGF may not be as effective and as selective as ADCs targeting membrane-bound antigens.

A more recent report targeting the membrane-bound receptor-2 for VEGF (VEGFR-2) demonstrated significant reduction in CNV area in a rat CNV model (6). Pigment epithelium derived factor (PEDF), a potent inhibitor of angiogenesis (7), was encapsulated in nanoliposomes conjugated to the peptide ATWLPPR which specifically targets VEGFR-2. Following intravitreal injection of the preparation, neovascular area in rat CNV lesion induced by laser was reduced by over 70% when compared to control, and 50% more effective when compared to PEDF encapsulated in nanoliposomes without conjugation with the peptide, supporting more efficient targeting of abnormal neovascular vessels by the immune-toxin complex.

In addition to VEGF-related antigen targets, several proteins including intercellular adhesion molecule-1 (ICAM-1) (3), E-selectin (3), CD44 (3), Endoglin (CD105) (8), and integrin αvβ3 (9) have been reported to be up-regulated in CNV lesions and some have served as targets for immune-toxin complex for potential treatment of CNV.

Endothelial cells in CNV membranes surgically excised from patients with AMD as well as in CNV lesions induced by laser in monkeys had strong immunoreactivity of CD105, but not in normal choroiretinal tissues (10). This lead to the effort by Yasukawa *et al.* to study the *in vitro* effect of an immunoconjugate of anti-CD105 monoclonal antibody and dextran binding mitomycin C and demonstrated a specific inhibitory effect on proliferating human umbilical vein endothelial cells (HUVECs) (10). The same group later studied the effect of mitomycin C conjugated to a different monoclonal antibody, targeting integrin αvβ3, both *in vitro* and *in vivo* (11). Integrin αvβ3 represents an ideal CNV drug target because it is minimally expressed on normal resting blood vessels (12). The immunoconjugate not only enhanced inhibition of HUVECs proliferation, but also significantly inhibited the development of CNV in rats following laser treatment (11).

Since the 2006 FDA approval of ranibizumab (Lucentis®), a monoclonal antibody fragment (Fab) against VEGF-A for wet AMD with demonstrated clinical benefit over verteporfin, intravitreal injection of anti-VEGF therapies have become the standard of care to treat CNV in patients. Bevacizumab (Avastin®), the full length monoclonal antibody and parent of ranibizumab, which was first approved in 2004 for metastatic colon cancer, has been extensively used off label in the treatment of wet AMD patients due to its significant lower cost compared to ranibizumab. Based on a government sponsored comparative study, the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT Study), bevacizumab was shown to be non-inferior to ranibizumab in efficacy assessed by visual acuity in patients with wet AMD (13). Following the clinical success of ranibizumab and bevacizumab, another anti-VEGF molecule aflibercept (Eylea®) was approved by FDA in 2011 for wet AMD. Aflibercept is a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of human VEGF receptors 1 and 2.

Given the fact that the anti-VEGF drugs have such potent anti-angiogenesis effect and good clinical efficacy in CNV patients, the research effort in finding immune-toxin complex to specifically target the abnormal endothelial cells responsible for CNV has diminished in the past decade. It is conceivable, however, for retinal disease that involves pathological growth of a specific cell type with distinct protein markers, this drug targeting strategy may still play a role in finding effective treatment.

TREATMENT OF POSTERIOR CAPSULE OPACIFICATION

Posterior capsule opacification (PCO), also called secondary cataract, is the most frequent complication of cataract surgery. There is opacity in the posterior part of the lens capsule which

increases gradually with time. There is painless blurring of vision that also increases gradually with time as the opacity increases. PCO occurs in virtually all pediatric patients and approximately half of adult patients within 2 to 5 years after extracapsular surgery because of the proliferation of remnant lens epithelial cells on the interior lens capsule surface (14). The development of opacity is a direct result of formation of multiple epithelial cell layers and contraction of myofibroblast-like epithelial cells. Because of the greater proliferative potential of lens epithelial cells in younger patients, PCO occurs sooner and in almost every infant and young child having extracapsular surgery (14). Since the pathogenesis of PCO involves unwanted proliferation of the lens epithelial cells, the ADC approach to target this specific cell population and avoid side effects on other ocular tissues has been researched and one was proven effective in the clinic specifically discussed in greater detail below.

Goins *et al.* tested the effect of an anti-transferrin receptor immunotoxin linked to ricin on proliferating human and baboon lens epithelium *in vitro* (15). While the conjugate inhibited human cell proliferation in a dose-dependent manner at concentrations of 100 to 10,000 ng/mL *in vitro*, it had no significant effect on confluent or non-dividing lens epithelial cells.

Behar-Cohen *et al.* tested the ability of a conjugate (FGF2-SAP) of fibroblast growth factor (FGF2) and saporin (a ribosome inactivating protein) prepared by either chemical conjugation or genetic engineering to inhibit the growth of bovine epithelial lens cells *in vitro* (16). The disulfide-linked conjugate targets bovine epithelial lens cells which bear FGF2 receptor on their surface and induces cell death due to blockage of protein synthesis by saporin (17). The chemically produced FGF2-SAP was 10-times more cytotoxic than the genetically engineering conjugate against bovine epithelial lens cells. When FGF2-SAP was tested in a rabbit model post extracapsular extraction of the lens, it effectively inhibited lens regrowth following direct injection into the capsular bag (18). However, the treatment induced transient corneal edema and loss of pigment in the iris based on histologic analysis of ocular tissues, likely limiting its further testing in a clinical setting.

Kelleher *et al.* developed an immuno-toxin, a murine monoclonal antibody (4197X) linked to the cytotoxic subunit of the polypeptide ricin toxin (ricin A) named 4197X-RA, that specifically targets a glycoprotein epitope on the membrane surface of human lens epithelial cells (19). Following binding, the immunotoxin is internalized and the cells are killed by inhibition of protein synthesis. Following intracameral injection in rabbit eyes, 4197X-RA had an aqueous humor half-life of approximately 1 h and was cleared, like other large protein molecules, from the anterior chamber by aqueous humor outflow (20). When incubated at the low concentration of 50 ng/mL with remnant human lens epithelial cells on lens capsules obtained during cataract surgery, 4197X-RA inhibited protein synthesis and lens epithelial cell proliferation by 95% (19). The inhibitory effects persisted up to 3 weeks after removal of the immunotoxin from the cell culture medium. When experiments were performed to determine the cytotoxicity of unconjugated ricin A, the immunotoxin was 200-fold more potent than the pure toxin, supporting its specificity against the human lens epithelial cells.

In a phase I/II clinical investigation to test the safety and effectiveness of 4197-RA, also named MDX-RA, 23 adult patients having extracapsular cataract extraction by phacoemulsification received 50 units and 19 received 175 units of the immunotoxin (21). The immunotoxin formulated in a salt solution was instilled into the anterior chamber at the end of the cataract surgeries following removal of the natural opaque lens and insertion of artificial intraocular lens. At the 50 unit dose level, MDX-RA was well tolerated with a comparable safety profile to that of the placebo group, and proven to be effective in inhibiting PCO for up to 24 months post cataract surgery. At the 175 unit dose, there was a trend toward greater postoperative intraocular inflammation that was transient which confounded grading of lens opacification. Based on opacification assessment in the different treatment groups, the estimated incidence of ND:YAG capsulotomy surgeries to treat PCO 3 years post the cataract surgeries was 57% in placebo patients and 4% in patients receiving 50 units of MDX-RA. Kaplan-Meier estimates of the time to predicted Nd:YAG capsulotomy in the placebo and 50 unit groups were statistically significantly different ($p < 0.004$). With this result, Metarex, maker of MDX-RA, announced in late 1997 the initiation of Phase III trials of MDX-RA to involve 680 patients undergoing primary cataract surgery at approximately 60 sites in the US (22).

As part of the phase III trial, two doses of MDX-RA were tested (23). In the eight patients who received 50 units doses and nine patients who received 100 units doses, no gross corneal damage was observed and it was confirmed again that MDX-RA was efficacious in reducing PCO post cataract surgery. However, early postoperative flare, anterior chamber cell count, and corneal pachymetry were higher in toxin-treated patients than placebo controls. Even though the authors concluded that MDX-RA appeared to be sufficiently tolerated, it was troublesome that the low dose group had more postoperative inflammation than the higher dose. Since in high risk patients such as those with diabetes or uveitic syndrome there exists a tendency toward increased postoperative inflammation, the clinical usage of MDX-RA could be restricted in this population. When Metarex announced suspension of patient enrollment for the phase III trial in late 1998 per recommendation of the trial's independent safety committee, it was revealed that ocular adverse events affected 13 of the 565 patients enrolled, seven occurring in patients receiving placebo and six in patients receiving MDX-RA (24).

Currently, Nd:YAG laser capsulotomy remains the treatment of choice despite its association with severe sight-threatening complications including macular edema, retinal detachment, or increased intraocular pressure (25,26). For an immunotoxin therapy to succeed, it appears that the targeted inhibition of lens epithelial cells results in good efficacy but it will have to overcome the hurdle of good tolerability in the eye with adverse events that are only transient and very mild in nature.

TREATMENT OF PROLIFERATIVE VITREORETINOPATHY

Proliferative vitreoretinopathy (PVR) is a complication that occurs after 5–10% of surgeries for rhegmatogenous retinal detachment (RRD) and can lead to blindness (27). PVR is characterized by extensive proliferative tissues on the surfaces of the retina and within the vitreous. Fibrous tissue that is scar-like forms in the vitreous and contains fibroblasts derived from retinal pigment epithelial cells or glial cells (27). Innate immunity is also thought to play a role in disease pathogenesis (28). Together these pathological processes represent potential drug targets.

Active drug targeting through immunoconjugates presents a particularly attractive option for preventative or therapeutic intervention for PVR. The potential use of immunotoxins directed against the membrane marker, transferrin receptor, that is associated with cell proliferation has been investigated as a potential therapeutic option for PVR. Exposure of cultures of proliferating human pigmented retinal epithelial (RPE) cells to immunotoxins composed of a monoclonal antibody directed against transferrin receptor and conjugated to ricin A was able to inhibit DNA synthesis and to significantly decrease the number of proliferating RPE cells (29,30). Using a collagen-gel medium to simulate vitreous, this immunotoxin was shown to inhibit fibroblast proliferation *in vitro* (31). The potential for these *in vitro* studies to translate to the clinic was supported by data from vitreous and subretinal fluid obtained from PVR patients. These clinical samples were shown to have strong expression of transferrin receptor through immunocytological examination using monoclonal antibodies to transferrin receptor while epiretinal membranes were shown to have low levels of expression (32). These data supported the potential to target this membrane antigen through an immunotoxin as a therapeutic agent.

More than a decade later these observations have yet to develop into a viable therapeutic option.

CONCLUSIONS

Modern medicine is an ever changing science undergoing development along with advancement in basic sciences and technology. As research and clinical experience continue to expand our knowledge base and reveal new molecular targets for disease treatment, we may see an expansion of research in building and testing immunotoxin conjugates, and subsequently wider application of this approach to treat ocular diseases beyond the three discussed in this review. FDA approved the first therapeutic monoclonal antibody, muromonab, in 1986 for use as an immunosuppressant in organ transplants. It took 20 years, until 2006, to see the first approval of a monoclonal Fab in ophthalmology, specifically, ranibizumab (Lucentis®) for the treatment of wet AMD. The first ADC approved by FDA in 2001 was gemtuzumab ozogamicin (Mylotarg®) for the treatment of acute myelogenous leukemia which was subsequently withdrawn due to safety issues related to the stability of the ADC. To date only two ADC are currently marketed, brentuximab vedotin (Adcetris®) and trastuzumab emtansine (Kadcyla) although many other ADC candidates are in clinical testing. While the opportunities for ADC are emerging in the treatment of diseases with a proliferative component, ideally, ophthalmology opportunities will be identified in parallel and not lag 20 years behind systemic therapy as was the case with antibody therapy.

Since the eye is such a complex and delicate organ, the key challenge faced by any medical therapy is limiting adverse effects, in particular for those that require intraocular drug administration as is the case for CNV, PCO, and proliferative vitreoretinopathy. Compared to the treatment of cancer, risk tolerance for therapies to treat non-blinding ocular diseases is significantly lower, in particular when effective treatments are already available. This may explain the limited clinical investigation of immunotoxin drug candidates despite promising efficacy results observed *in vitro* and *in vivo* in animal models.

While immunotoxin conjugates by design target specific cell types associated with pathogenesis of the disease at hand, unexplained adverse finding in clinical trials for MDX-RA despite its low incidence is discouraging and warrants thorough investigation. It seems that the early clinical development lacked sufficient exploration of dose response both in efficacy and safety response. It is also unclear if there has been sufficient data generated to understand stability of the conjugate once injected into the human eye and how is the conjugate or its degradants cleared from the eye at what rate. Even if drug candidates advance through preclinical ocular safety testing which is typically conducted in young healthy animals that are mostly inbred and homogenous, it should be kept in mind that many ocular diseases occur in older patient populations with comorbidity such as diabetes and cardiovascular diseases which complicate the microenvironment in the eye making them more prone to inflammation. Such scientific questions may be critical to develop successful immunotoxins for ophthalmological indications that are not only efficacious but also well tolerated in the eye.

REFERENCES

1. Sassoon I, Blanc V. Antibody-drug conjugate (ADC) clinical pipeline: a review. Methods Mol Biol. 2013;1045:1–27.
2. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med. 2008;358(24):2606–17.
3. Shen WY, Yu MJ, Barry CJ, Constable IJ, Rakoczy PE. Expression of cell adhesion molecules and vascular endothelial growth factor in experimental choroidal neovascularisation in the rat. Br J Ophthalmol. 1998;82(9):1063–71.
4. Husain D, Ambati B, Adamis AP, Miller JW. Mechanisms of age-related macular degeneration. Ophthalmol Clin N Am. 2002;15(1):87–91.
5. Mayo GL, Melendez RF, Kumar N, McKinnon SJ, Glickman RD. Antibody-targeted photodynamic therapy. Am J Ophthalmol. 2003;136:1151–2.
6. Li T, Zhang M, Han Y, Zhang H, Xu L, Xiang Y. Targeting therapy of choroidal neovascularization by use of polypeptide- and PEDF-loaded immunoliposomes under ultrasound exposure. J Huazhong Univ Sci Technolog Med Sci. 2010;30(6):798–803.
7. Dawson DW, Volpert OV, Gillis P, Crawford SE, Xu H, Benedict W, *et al.* Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. Science. 1999;285(5425):245–8.
8. Kimura H, Yasukawa T, Tabata Y, Ogura Y. Drug targeting to choroidal neovascularization. Adv Drug Deliv Rev. 2001;52(1):79–91.
9. Friedlander M, Theesfeld CL, Sugita M, Fruttiger M, Thomas MA, Chang S, *et al.* Involvement of integrins alpha v beta 3 and alpha v beta 5 in ocular neovascular diseases. Proc Natl Acad Sci U S A. 1996;93(18):9764–9.
10. Yasukawa T, Kimura H, Tabata Y, Miyamoto H, Honda Y, Ikada Y, *et al.* Active drug targeting with immunoconjugates to choroidal neovascularization. Curr Eye Res. 2000;21(6):952–61.
11. Kamizuru H, Kimura H, Yasukawa T, Tabata Y, Honda Y, Ogura Y. Monoclonal antibody-mediated drug targeting to choroidal neovascularization in the rat. Invest Ophthalmol Vis Sci. 2001;42(11):2664–72.
12. Brooks PC, Clark RA, Cheresh DA. Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science. 1994;264(5158):569–71.
13. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, *et al.* Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388–98.
14. Goins KM, Ortiz JR, Fulcher SF, Handa JT, Jaffe GJ, Foulks GN, *et al.* Inhibition of proliferating lens epithelium with antitransferrin receptor immunotoxin. J Cataract Refract Surg. 1994;20(5):513–6.
15. Tarsio JF, Kelleher PJ, Tarsio M, Emery JM, Lam DM. Inhibition of cell proliferation on lens capsules by 4197X-ricin A immunoconjugate. J Cataract Refract Surg. 1997;23(2):260–6.
16. Behar-Cohen FF, David T, Buechler Y, Nova MP, Houston LL, Pouliquen YM, *et al.* Cytotoxic effects of FGF2-saporin on bovine epithelial lens cells in vitro. Invest Ophthalmol Vis Sci. 1995;36(12):2425–33.
17. David T, Tassin J, Lappi DA, Baird A, Courtois Y. Biphasic effect of the mitotoxin bFGF-saporin on bovine lens epithelial cell growth: effect of cell density and extracellular matrix. J Cell Physiol. 1992;153(3):483–90.
18. Behar-Cohen FF, David T, D'Hermies F, Pouliquen YM, Buechler Y, Nova MP, *et al.* In vivo inhibition of lens regrowth by fibroblast growth factor 2-saporin. Invest Ophthalmol Vis Sci. 1995;36(12):2434–48.
19. Kelleher PJ, Tarsio JF, Clark DS. Cytotoxic effects of a monoclonal antibody-ricin A immunotoxin on human ocular cells in culture. ARVO abstract 2562. Invest Ophthalmol Vis Sci. 1992;33:1168.
20. Crosson CE, Kelleher PJ, Lam DM. Ocular pharmacokinetics of lens epithelial cell-specific immunotoxin 4197X-RA. Exp Eye Res. 1992;55(1):87–91.
21. Clark DS, Emery JM, Munsell MF. Inhibition of posterior capsule opacification with an immunotoxin specific for lens epithelial cells: 24 month clinical results. J Cataract Refract Surg. 1998;24(12):1614–20.
22. Castillo E. MDX-RA Medarex Inc. IDrugs. 1998;1(4):476–9.
23. Meacock WR, Spalton DJ, Hollick EJ, Boyce JF, Barman S, Sanguinetti G. Double-masked prospective ocular safety study of a lens epithelial cell antibody to prevent posterior capsule opacification. J Cataract Refract Surg. 2000;26(5):716–21.
24. PR Newswire. Medarex suspends patient enrollment in phase III trial of MDX-RA cataract product. 1998 December 15. Available from: http://www.thefreelibrary.com/_/print/PrintArticle.aspx?id=53401608.
25. Elgohary MA, Dowler JG. Incidence and risk factors of Nd:YAG capsulotomy after phacoemulsification in non-diabetic and diabetic patients. Clin Experiment Ophthalmol. 2006;34(6):526–34.
26. Schubert HD. Vitreoretinal changes associated with rise in intraocular pressure after Nd:YAG capsulotomy. Ophthalmic Surg. 1987;18(1):19–22.
27. Sadaka A, Giuliari GP. Proliferative vitreoretinopathy: current and emerging treatments. Clin Ophthalmol. 2013;6:1325–33.
28. Zhang W, Tan J, Liu Y, Li W, Gao Q, Lehmann PV. Assessment of the innate and adaptive immune system in proliferative vitreoretinopathy. Eye. 2012;26(6):872–81.
29. Jaffe GJ, Earnest K, Fulcher S, Lui GM, Houston LL. Antitransferrin receptor immunotoxin inhibits proliferating human retinal pigment epithelial cells. Arch Ophthalmol. 1990;108(8):1163–8.
30. Baudouin C, Brignole F, Fredj-Reygrobellet D, Nègre F, Bayle J, Gastaud P. Transferrin receptor expression by retinal pigment epithelial cells in proliferative vitreoretinopathy. Invest Ophthalmol Vis Sci. 1992;33(10):2822–9.
31. Hermsen VM, Fulcher SF, Spiekerman M, Phinizy JL, Di Tullio NW. Long-term inhibition of cellular proliferation by immunotoxins. Arch Ophthalmol. 1990;108(7):1009–11.
32. Handa JT, Houston LL, Jaffe GJ. The antiproliferative effect of a transferrein-toxin on human retinal pigment epithelial cells and rabbit fibroblasts. Invest Ophthalmol Vis Sci. 1993;34(12):3419–28.