The Role of Xenobiotic Transporters in Ophthalmic Drug Delivery

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ABSTRACT - The eye is a very complex sensory organ consisting of numerous structures to coordinate the function of sight. It has a series of physical and chemical barriers to help maintain its homeostasis, and mediate environmental exposures. Transporters in the eye play a very important role in maintaining homeostasis by facilitating the movement of ions, nutrients and xenobiotics to various tissues in the eye, especially to non-vascular tissues like the lens and cornea. They also ensure proper cell signaling by shuttling neurotransmitters within the retina. Thus, they are expected to play an important role in determining the ocular exposure of drugs and other pharmacotherapeutics. However, the role of ocular transporters in ophthalmic drug delivery and their clinical relevance has not been well characterized. The purpose of the present review is to summarize the current evidence in the literature on ocular drug transporters and their role in ocular drug delivery, with the emphasis predominantly on their role in ocular pharmacokinetics.

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INTRODUCTION

The role of drug transporters in the gastrointestinal (GI) tract, lymphatic system, blood brain barrier (BBB), liver and kidneys is well known and documented [1-6]. Transporters can affect multiple aspects of drug disposition and can result in potential drug-drug interactions, lack of efficacy, toxicity and drug related adverse events relative to exposure levels.

Drug transporters have the potential to alter the efficacy of a molecule at the site of action, for example, in the liver or the brain [1]. The brain parenchymal cells contain transporters including P-glycoprotein (P-gp), which can efflux drugs, thus lowering their concentration at the site of action and ultimately decreasing their efficacy [2-5]. Conversely, facilitative transporters like organic cation transporters (OCTs) or dopamine transporter (DAT) would improve drug efficacy by transporting the molecule into or out of neurons, thus, increasing their target site concentration [5-7]. Although topical ocular administration is the primary method for delivery of therapeutics to the eye, not much is understood about the clinical relevance of transporters in ocular drug disposition. The eye, being responsible for the sense of vision, has evolved into an organ with complex anatomy and physiology to maintain homeostasis and ensure effective functioning. The mechanisms include transporters, ion channels, and physical barriers which act as defense mechanisms and help maintain concentrations of essentials nutrients. While there are good reviews on ocular drug transporters, little is known about their role in ocular drug efficacy, ocular pharmacokinetics and ocular safety issues [8-10]. In the present article, we review the current evidence in the literature on ocular drug transporters and their role in ocular drug delivery, with the emphasis predominantly on their role in ocular pharmacokinetics. We will also discuss their future relevance and the need to better understand their role in ocular drug delivery.

ANATOMY OF THE EYE

The eye is a very complex structure that is closely connected to the rest of the body through its

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vascular and neural networks [11, 12]. Its unique anatomy and physiology place several constraints on the delivery of drugs to the eye because of its innate nature to protect itself and, ultimately, the vision from exogenous substances [11]. Therefore, it is critical to understand the anatomy and physiology of the eye to design adequate and effective drug delivery systems. The objective of this review is not to cover in detail the anatomy of the eye since there are excellent reviews and articles that cover this topic in detail. We recommend the reader review these references for further detail [11, 13-33]. Ocular drug disposition is not only influenced by the complex anatomy, but also by lacrimation, tear film dilution and tear turnover mechanisms [34]. The presence of melanin and ocular transporters, as well as the blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) significantly affect ocular drug disposition [12, 35-39] [40-45].

There are several routes of ocular drug delivery (Table 1). The benefits and challenges of

Table 1. Summary of Route of Administration, Benefits, and Challenges in Ocular Delivery (modified from Gaudana *et al.* [12] with permission).

Route	Benefits	Challenges	Application in the treatment of diseases
Oral/Systemic	Patient compliant and noninvasive route of administration	BAB, BRD, high dosing causes toxicity, BA <2%	Scleritis, episcleritis, CMV retinitis, PU
Topical	High patient compliance, self-administrable and noninvasive	Higher tear dilution and turnover rate, cornea acts as barrier, efflux pumps, BA <5%	Keratitis, uveitis, conjunctivitis, scleritis, episcleretis, blepharitis
Intravitreal	Direct delivery to the vitreous and retina, sustains drug levels, evades BRB	Retinal detachment, hemorrhage, cataract, endophthalmitis, patient incompliance	AMD, PU, BRVO, CRVO, DME, CME, UME, CMV retinitis
Intracameral	Provides higher drug levels in the anterior chamber, eliminates usage of topical drops, reduces corneal and systemic side effects seen with topical steroid therapy	Toxic anterior segment syndrome (TASS) and toxic endothelial cell destruction syndrome (TECDS)	Anesthesia, prevention of endophthalmitis, inflammation and pupil dilation
Subconjunctival	Delivery to anterior and posterior segment, site for depot formulations	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Subtenon	High vitreal drug levels, relatively nonivasive, fewer complications unlike intravitreal delivery	RPE, chemosis, subconjunctival hemorrhage	DME, AMD, RVO, uveitis
Retrobulbar	Administer high local doses like anesthetics, more effective than peribulbar, minimal influence on IOP	Retrobulbar hemorrhage, globe perforation, respiratory arrest	Anesthesia
Posterior juxtascleral	Safe for delivery of depot formulations, sustain drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier	AMD

BA bioavailability, BAB blood–aqueous barrier, BRB blood–retinal barrier, AMD age-related macular degeneration, DME diabetic macular edema, BRVO branched retinal vein occlusion, CRVO central retinal vein occlusion, RVO retinal vein occlusion, CME cystoid macular edema, UME uveitic macular edema, CMV cytomegalovirus, IOP intraocular pressure, TASS toxic anterior segment syndrome, TECDS toxic endothelial cell destruction syndrome, RPE retinal pigmented epithelium, PU posterior uveitis

the various routes of administration [12] as well as the complexity of ocular pharmacokinetics [46] have been reviewed elsewhere. Briefly, topical ocular administration is generally the preferable route for patients based on ease of administration and can be used for the treatment of a variety of ocular diseases. However, invasive techniques (i.e. intravitreal or intracameral injections) need to be employed for diseases such as age-related macular degeneration (AMD), retinal vein occlusion, or macular edema.

TRANSPORTERS AND THEIR ROLE IN FUNCTIONING OF THE EYE

The eye is an important sensory organ and is one of the very few which come in direct contact with the environment. One can therefore appreciate the role of transporters as a defense mechanism preventing the entry of foreign and/or possibly toxic xenobiotics into the eye, which could disrupt vision [8-10]. To date transporters in the eye and their role in ophthalmic drug delivery have not been well characterized.

In addition to serving as a defensive mechanism, transporters also help maintain pH, ionic and osmotic equilibrium in the eye [47-50]. Membrane transporters regulate the levels of ions, glucose and vitamins to maintain homeostasis in the eye [51]. A disruption of these mechanisms leads to various conditions including cataract [51]. In a similar fashion, inhibition and activation of transporters in various matrices of the eye could lead to safety issues. For example, inhibition of the glucose transporter, found in the lens and the conjunctiva could lead to disruption of the homeostasis of the lens [51].

Cellular transporters play an important role in the disposition of drugs at the site of therapeutic action. An efflux transporter could limit the amount of drug reaching the target ocular tissue limiting their efficacy, while an uptake transporter could result in elevated levels of a drug in a particular tissue. Ophthalmic drug transporters have been the subject of investigation and the published literature indicates that they play a role in ophthalmic drug delivery. In the following sections we present information on ocular transporters known to be expressed in the eye, dividing them into anterior and posterior segments. A brief review is provided, of *in vitro* and *in vivo* techniques used to study transporters and evidence of the role of ocular transporters.

Current Technologies to Study Ocular Drug Transporters

In vitro Methodologies

A variety of *in vitro* techniques have been employed to investigate the expression, localization and function of transporters. Techniques like PCR, Western blotting and immunohistochemistry are used to study the expression of transporters and their localization in various tissues [52, 53]. To determine their functionality, current technologies on transporters utilize either inhibition or substrate transport studies (done as a monolayer or in suspension). Transport studies with compounds in transfected cell lines, vesicles from insects, transporter cDNA expressing insect membranes and oocytes are used to identify the substrate nature of compounds and to determine their kinetics [54-57]. Inhibition studies can also be conducted using the afore mentioned techniques. These studies reveal the substrate or inhibitor nature of a compound, as well as the nature of inhibition (competitive against non-competitive).

Corneal cell lines from humans and animal species [49, 52, 53, 58-63], are available to study drug permeability and drug transporters. The role of transporters in conjunctival cell lines like HCjE (human conjunctival epithelial cells), CJVE (rabbit conjunctival epithelial cells) has also been demonstrated [58, 59, 64]. The studies with HCLE (human cornea limbal epithelial cells) and HCjE cells were the first to show the expression of OCTN1 and OCTN2 in these cell lines and demonstrated the role of OCTN2 in the active transport of L-carnitine transport. The studies with CJVE cell line demonstrated the function of novel sodium dependent and sodium independent transport mechanisms for synthetic and endogenous opioids. The permeability of compounds across retinal cell lines like ARPE-19 and retinoblastoma cells [65, 66] has also been investigated. The study revealed the presence and expression of a new oligopeptide transporter (SOPT2), which transported synthetic opioid (DADLE) with partial sodium dependence. Such *in vitro* systems become useful to determine the permeability of compounds and the role of transporters across these barriers. The use of *in vitro* studies to characterize the

capacity of a compound to act as a substrate or inhibitor of a particular transporter provides information about its ability to reach the intended site of action. Furthermore, these studies provide understanding about the kinetics of the process, the possible interactions and the potential clinical relevance.

In vivo and Ex vivo Methodologies

Both *in vivo* and *ex vivo* methodologies are also used to study transporters. Inhibition and saturability studies are done with wild type animals to determine *in vivo* kinetics of transporters. Drug-drug interaction potential can also be tested using transporter knock-out or transgenic animals [67-71], which are deficient in a particular transporter compared to the wild type animal. Studying the pharmacokinetics of the compound in the two models simultaneously gives a measure of the contribution of the transporter to the maximal concentration (C_{max}) and area under the concentration-time curve (AUC) of the compound. *In vivo* studies to investigate the role of ocular transporters have been conducted in rabbits [72]. The role of P-gp was well demonstrated by investigating the pharmacokinetics of quinidine and erythromycin in rabbits [72, 73]. The role of MRP5 in rabbits was also studied using acyclovir as a model substrate [53]. Potential ocular or ocular-systemic drug-drug interactions can also be investigated using such *in vivo* and *ex vivo* methodologies [74, 75]. Some of the ocular tissues including cornea and retina can be excised and the permeability of compounds studied across the sections. *Ex vivo* studies with isolated cornea [49, 61, 62] and isolated retina [65, 76] have been conducted to determine the permeability of molecules and the role of transporters.

Some of the new technologies being explored to study transporters involve the use of antibodies to knock out transporters and study their role in drug pharmacokinetics [77]. A second technique is the inhibition of transporters, using siRNA [78, 79], to study the role of transporters. These are fairly new techniques which have not been thoroughly investigated for ophthalmic drug delivery. *In vitro* and *ex vivo* techniques can be used to rank order compounds. In conjunction with *in vivo* studies, the *in vitro* and *ex vivo* data can be used to conduct *in vitro-in vivo* correlations (IVIVC). Further refinement of these techniques needs to be conducted to adapt them to study the role of transporters in the eye.

Transporters in the Anterior Segment of the Eye

The tissues/matrices in the anterior segment of the eye are conjunctiva, cornea, aqueous humor, lens, lens capsule, iris, ciliary body and trabecular meshwork. Transporters are known to be expressed in the conjunctiva, cornea, lens, iris and ciliary body. However, our major focus will be on transporters in the conjunctiva and cornea while only mentioning the transporters in the lens and ICB [47, 49, 51, 80-84].

Drug Transporters in the Conjunctiva

As most of the topical ocular administered drugs and xenobiotics come in contact with the conjunctiva, it is very well equipped to regulate their absorption into the eye and presents one of the very first barriers to topical ocular drug delivery. Yang *et al.* demonstrated the role of P-gp in limiting propranolol transport in rabbit conjunctival epithelial cells [80]. They also demonstrated the expression, localization and function of MRP1 in rabbit conjunctival epithelial cells [81]. Ueda *et al.* demonstrated the function of organic cation transporting system in excised pigmented rabbit conjunctiva [47]. Garrett *et al.* demonstrated the expression and localization of OCTN1 and OCTN2 in human corneal and conjunctival cells, as well as their role in carnitine uptake [59]. An excellent review on the role of conjunctiva in ocular drug delivery is available [48]. Figure 1 shows some of the transport processes that take place in the conjunctival epithelium.

Presence and activity of other relevant transporters like PepT1 and PepT2 in pigmented rabbit conjunctiva was reported by Sun *et al.* [85], while Basu *et al.* demonstrated their function in cultured rabbit conjunctival epithelial cells [86]. Other transporters and ion and fluid transport mechanisms exist in the conjunctiva.

Drug Transporters in the Cornea

Transporters in the corneal epithelium are outlined in Figure 2 [9]. There are both uptake and efflux transporters, for both large and small molecules which can influence drug exposures. These transporters serve to transfer molecules across the epithelium in either direction (towards the tear film or towards the aqueous humor). Studies on

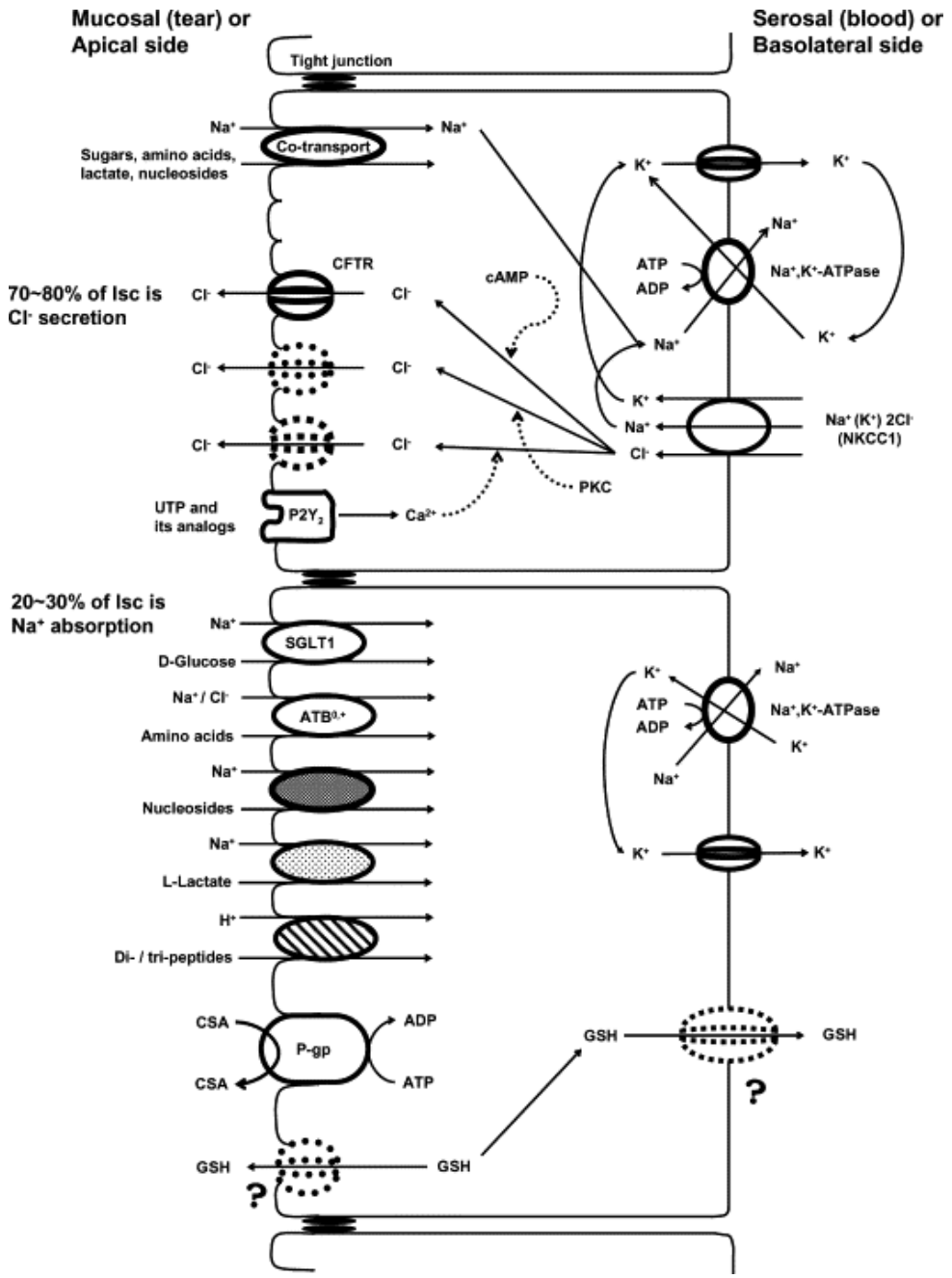

Figure 1: Ion and solute transport processes in the conjunctiva. Some transport processes (e.g. Na+-independent, carrier-mediated processes) are not shown for clarity, especially those localized at the serosal (or basolateral) aspect of the conjunctiva. Reproduced from Hosoya *et al.* [48] with permissions.

acyclovir and acyclovir prodrugs demonstrated not only that peptide transporters like PepT1 are present on the corneal epithelium, but also play an active role in the transport of these prodrugs. The presence of a facilitative transporter, OATP2A1, has been demonstrated in cornea, conjunctiva, iris and ciliary body and its role in the permeability of both latanoprost and its free acid metabolite was reported [87]. Vakkalagadda *et al.* demonstrated the expression and functionality of LAT1 (sodium independent neutral amino acid transporters) in excised rabbit cornea and the SIRC cell line [49].

The role of efflux transporters like MRP1, MRP2 and MRP5, using MDCK cell lines over-

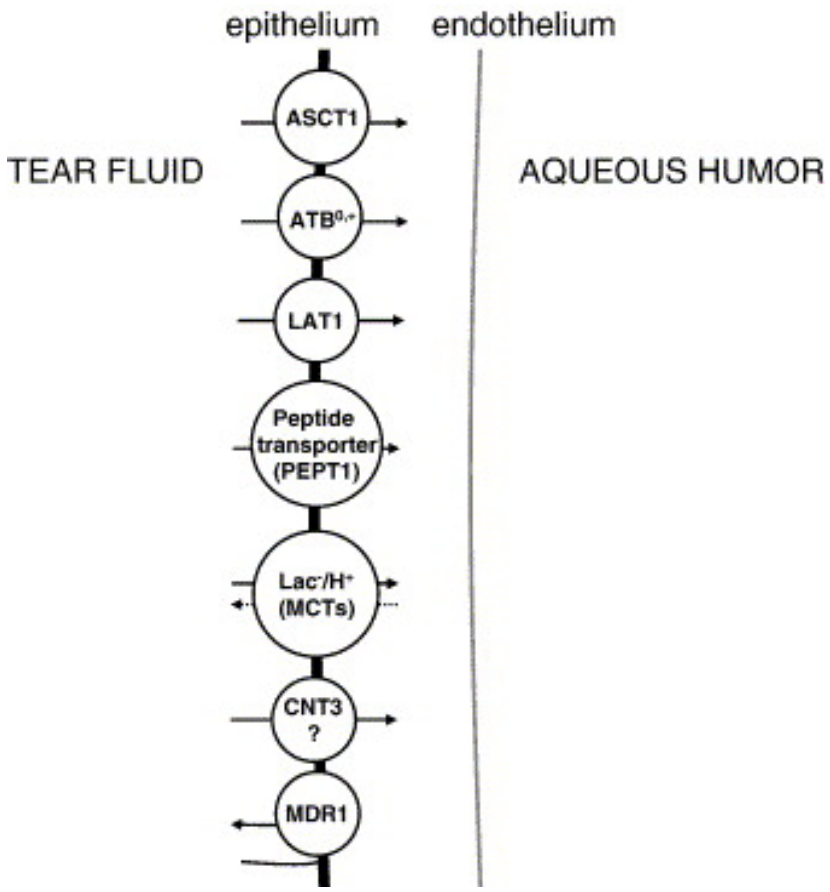

Figure 2: Currently known functional transporters in the corneal epithelium. MDR1- P-glycoprotein; CNT3- Concentrative nucleoside transporter 3; PEPT1- Peptide transporter1; MCTa- Monocarboxylate transporter a; LAT- L- amino acid transporter; ATB- Sodium dependent amino acid transporter; ASCT1- Alanine Serine Cysteine Transporter1. Reproduced from Mannermaa *et al.* with permissions [9].

expressing these transporters and excised rabbit cornea in the transport of prostaglandin analogues was also demonstrated [82]. The role of MRP5 in ocular uptake has been shown using acyclovir in human and rabbit corneal epithelial cells as well as *ex vivo* and *in vivo* studies in rabbits [53]. Furthermore, the efflux nature of P-gp and MRP2 in rabbit cornea and their action on erythromycin have also been reported [73, 88, 89]. Vellonen *et al.* reported significant expression and localization of MRP1, MRP5 and BCRP in human corneal epithelium; with no significant expression of MDR1 (P-gp), MRP2, MRP3, MRP4 and MRP6 [90], which agrees with previous reports [91].

Vellonen *et al.* [90] studied the expression and function of monocarboxylate transporters in human corneal epithelial and rabbit cornea cells. They demonstrated that MCT1 and MCT4 played a role in L-lactic acid and benzoic acid permeability and could be subjected to inhibition by employing inhibitors [92].

Drug Transport in the Iris-ciliary Body (ICB) and the Lens

The lens is rich in nutrient transporters and ion channels to maintain the osmotic and refractive nature. A glucose transporter was shown to be present in the ciliary body of human and rat eye [93], and a nucleoside transporter was demonstrated in rabbit ICB [94]. Amino acid transporters, potassium chloride co-transporters (KCC), glucose transporter (GLUT1 and GLUT 3) and vitamin C transporter have been identified in the lens to date [50, 51, 83, 84, 95, 96]. The presence and function of these and other transporters in the anterior segment tissues indicate an integral role for the transporters in the functioning of the eye.

Transporters in the Posterior Segment of the Eye

Drug Transporters in the Retinal Pigmented Epithelium (RPE) and Retina

P-gp expression and functional activity has been identified in RPE [72, 97-99]. For instance, P-gp was detected (presence of mdr1 mRNA) by RT-PCR in cultured human RPE and it was suggested that the basolateral P-gp would protect the neural retina by expelling unwanted substances from the subretinal space [97]. However, it was also reported that P-gp was present in the apical surface as well, which could indicate additional functions in the RPE [97]. Similarly, using the same approach it was determined that P-gp is expressed in the human RPE cells lines: D407 and h1RPE, but not in ARPE19. However, functional P-gp was only demonstrated in D407 cells [98].

MRP1 was expressed and identified in human retinal pigment epithelial (ARPE-19) cell line and primary cultures of human retinal pigment epithelial (HRPE) cells [100], as well as in the choroidal side of the outer BRB [101]. In the case of peptide transporters, ASCT2 (SLC1A5) was expressed in retinal Muller cells and it was suggested that this transporter also serves as an effluxer of D-serine [102]. Similarly, PepT-2 mRNA has been reported on retinal Muller cells [103] and also on retina when vitreous clearance of cephalosporins was studied using ocular microdialysis [104]. Furthermore, PHT1 has been reported to be expressed in bovine RPE (BRPE), human RPE (HRPE) cells, ARPE-19 (human RPE cell line), and bovine and human neural retina [105], while PEPT2 and PHT2 were only expressed in bovine and human retina [105]. It has also been reported that PEPT2 was identified on the RPE side facing the blood compartment [106, 107] and on the retina side facing the vitreous humor [103, 107]. For this reason, PEPT2 has been proposed as a target to increase intracellular concentrations in the retina following intravitreal administration or to enhance retinal concentrations following systemic administration [107].

Retina is considered to be the ocular tissue with the highest metabolic rate per weight [108]. This is primarily because the retina is considered an outgrowth of the developing brain and has similar neural constituents that require an active protection system as seen in brain tissue [109]. One of these protection systems is the blood-retinal barrier (BRB), which is formed by tight junctions between the cells of the RPE and the endothelial cells of the capillaries and prevents the leakage of protein or fluid from the vasculature into the retina [110]. For instance, Figure 3 represents the transporters at another barrier- a barrier to drug delivery to the back of the eye, more popularly known as the BRB [9]. This figure shows the transporters at the outer and inner blood-retinal barriers. There are multiple uptake and efflux transporters and the localization of P-gp on both surfaces of the epithelium is puzzling and interesting. The transport across this epithelium is also a combination of paracellular, transcellular and active transport. This barrier is more complex than the BAB and represents a major hurdle for drug delivery to the back of the eye, both from topical ocular and non-topical delivery [9].

Furthermore, various glucose transporters facilitate the transport of glucose across the blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) [34, 95]. For instance, GLUT1, GLUT3 and GLUT4 are high affinity glucose transporters, while GLUT 2 is considered a low affinity glucose transporter. GLUT5 is a high affinity fructose transporter [95]. In the case of GLUT 1 it was reported in RPE, choroid, par plasma, lens fiber cells and retinal Mueller cells [111]. It has also been reported that amino acid transporters including glutamate, glycine, GABA, proline and tryptophan are present on the retina [107, 112]. The GLUT1 glucose transporter is expressed in endothelial and epithelial barriers like the retinal capillary endothelium and RPE, which was studied in diabetic and nondiabetic human eyes [113].

Monocarboxylic acid transporters (MCTs), which transport pyruvate and lactate, among other carboxylic acids have been found in the retina [107, 114, 115]. Specifically, MCT1 has been reported on the apical membrane of rat RPE, while MCT3 has been described on the basolateral membrane [116]. Recently, a folate receptor (FR), which is a specialized carrier-mediated active transporter system, has been described in human derived retinoblastoma cell line (Y-79) [117]. Similarly, in the same cell line biotin has been reported to be transported via a human sodium dependent multivitamin transporter (hSMVT), which is a specialized carrier-mediated system for biotin uptake into retinoblastoma cells [118]. The same research group also reported a riboflavin transporter

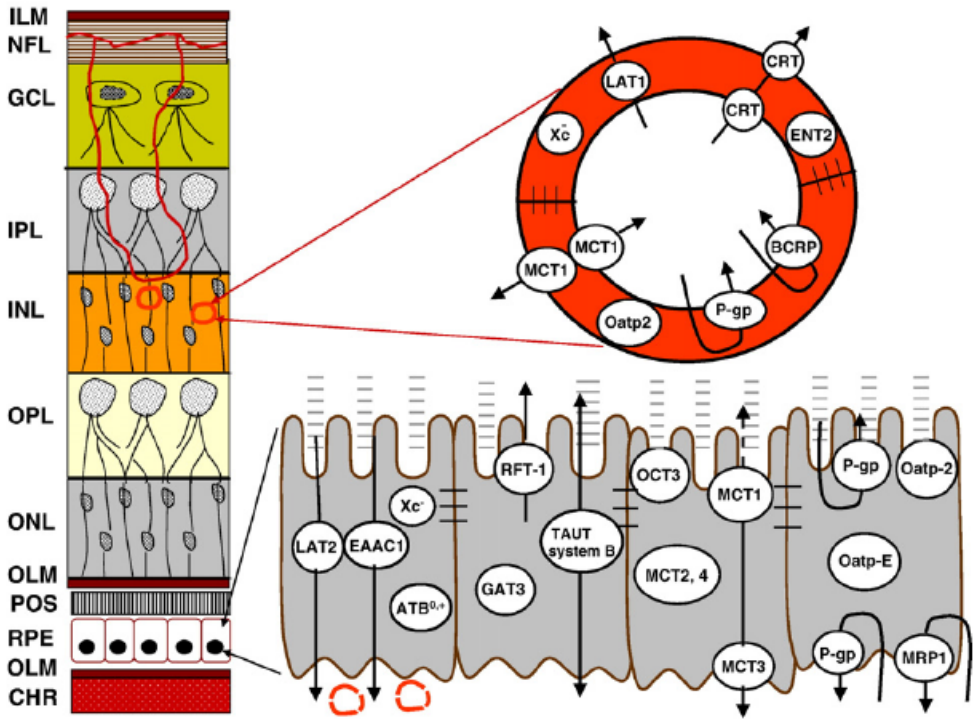

Figure 3: Schematic picture of the retina and of the transporters of outer and inner blood-retinal barriers. Abbreviations: ILM- inner limiting membrane; NFL- nerve fiber layer; IPL- inner plexiform layer; PL- outer plexiform layer; ONL- outer nuclear layer; OLM- outer limiting membrane; POS- photoreceptor outer segments; RPE- retinal pigment epithelium; BM- Bruchs membrane; CHR- choroids; MDR1- P-glycoprotein; MRP1- Multidrug resistance associated protein 1 transporter; OCT- Organic cation transporter; MCTa- Monocarboxylate transporter a; LAT- L- amino acid transporter; ATB- Sodium dependent amino acid transporter; OATP- Organic anion transporting polypeptide; BCRP- Breast cancer resistance protein transporter; CRT- Creatine Transporter; ENT- Equilibrative nucleoside transporter; GAT- gamma amino butyric acid transporter; TauT- Taurine Transporter. Reproduced from Mannermaa *et al.* [9] with permission.

in Y-79 cells, which is a transporter system that is regulated by protein kinase A and Ca^{2+}/calmodulin pathways [119].

It needs to be mentioned that the water transport across the RPE and other ocular tissues has been reviewed elsewhere [109]. Briefly, the water transport across the RPE is mediated via an active solute-linked water transport via monocarboxylate transporter (MCT1 and MCT3) and via osmotic and hydrostatic forces that determine the other two passive mechanisms for water transport [109].

ROLE OF TRANSPORTERS IN OCULAR DRUG DELIVERY - FRONT AND BACK OF THE EYE

As stated above there is the presence of efflux and influx transporters in various ocular cell lines and tissues. While the efflux transporters lower the bioavailability of a drug by effluxing it out of the cell membrane and cytoplasm, the influx transporters will facilitate the translocation of a drug across biological membranes. Therefore, it can be understood that transporters play a crucial role for ocular drug delivery. It needs to be understood that the permeation of a drug through the eye will be dependent on the passive transport of the administered drug and its concentration gradient [9]. Keeping in mind that active transport is against the concentration gradient and needs energy, careful consideration needs to be taken for an ophthalmic drug, considering that transporter proteins may become saturated at high concentrations. This is highly relevant after intravitreal injection when there is a high local concentration in the vitreous humor. It needs to be mentioned that choroidal vessels present fenestrations from which a drug can

escape this vasculature and leak out to the RPE and then reach the neural retina and vitreous humor. Thus, a drug can enter the vitreous humor and retina via the retinal capillaries or the blood stream of the choroid [9, 120].

The gene expression of both uptake and efflux transporters in different parts of the eye was measured by Zhang *et al.* [121]. Based on their findings, MRP1 seems to be a more important efflux transporter for the eye compared to P-gp. However, as is the usual case, more attention has been devoted to P-gp than to MRP1 in functional assays. As far as the facilitative transporters are concerned, OATPs, PEPT2, OCTs, OCTNs seem to be important for the eye. Though the expression, presence and localization of these transporters have been studied by Zhang *et al.* [121], the functional activity of all these transporters has not been well characterized. In other words, the presence or expression of a transporter indicates that the transporters might be functionally active, but does not guarantee it. The functional activity also needs to be demonstrated.

As presented, many of the ocular transporters have been cloned and expressed in various ocular cell lines and tissues. Some of them are involved in various processes including absorption, distribution and excretion of ophthalmic drugs. Because this is a very active field of study, various drug delivery approaches are taken to develop more effective therapeutic agents. The challenges to effectively deliver drugs to the posterior part of the eye following topical ocular administration are well known. The first barrier is the high tear turnover rate which will wash off or dilute the dose of the administered drug causing precorneal loss [10]. Then, there is the presence of efflux and influx transporters in the eye, the blood-aqueous barrier (BAB) and blood-retinal barrier (BAB). Presented below will be various approaches that have been pursued to circumvent these issues. For example, transporter-targeted prodrug delivery has been utilized to improve bioavailability in the eye.

Efflux Transporters

Some of the efflux transporters that have been characterized in ocular cell lines and tissues include P-gp in cornea, conjunctiva and RPE cell lines [73, 80, 122-124]; MRP1 in rabbit conjunctival epithelial cells and RPE [81, 100], MRP2 [89] and MRP5 [53] in corneal epithelium; as well as BCRP [52] also in the corneal epithelium.

To date, the role of P-gp has been the most studied, as was the case with oral route of drug delivery. The localization and functional activity of P-gp and MRP in porcine eyes was demonstrated [101]. The molecular evidence and functional expression of MRP2 in human corneal epithelium and rabbit cornea and its role in ocular drug efflux was demonstrated [125]. Dey *et al.* [73] demonstrated the effect of P-gp in erythromycin pharmacokinetics in rabbit and human cornea. The corneal AUC of erythromycin in the presence of testosterone, a P-gp inhibitor, was significantly increased indicating a role for P-gp in influencing corneal drug bioavailability. MRP1 has not received much attention despite the evidence presented by Zhang *et al.* [121] and more studies are warranted. Some ophthalmic relevant drugs with their mode of administration along with the uptake and efflux transporters affecting their disposition is given in Table 2 [9].

Influx Transporters

In the case of ocular influx transporters there are mainly amino acid and peptide transporters [12]. For instance, ASCT1 (SLC1A4), a neutral amino acid transporter that belongs to the SLC1 gene family has been detected in rabbit cornea and in rPCEC (rabbit primary corneal epithelial cells) [63]. Similarly, ASCT2 (SLC1A5) was expressed in retinal Muller cells and it was suggested that this transporter also serves as an effluxer of D-serine [102]. The neutral and cationic amino acid transporter $B^{0,+}$ (SLC6A14) has been found to be expressed in rabbit cornea, rabbit corneal epithelium and human cornea and to be involved in the L-arginine transport across corneal epithelium [126] but also across pigmented rabbit conjunctiva [127]. Furthermore, the Na+-independent large neutral amino acid transporter LAT1 (SLC7A5) was identified in human and rabbit cornea [49], while LAT2 (SLC7A8) was identified in the posterior segment [using an *in vitro* human model using RPE cell line (hTERT-RPE)] [128] and in ARPE-19 cells where it was determined to be involved in L-phenylalanine transport [129].

The peptide transporters are proton coupled transporters that contribute to the translocation of di- and tripeptides across the epithelium [130] and are mainly classified into PepT1, PepT2 and peptide/histidine transporters (PHT1 and PHT2)

Table 2: Selected ocular drugs and suggested interactions with transporters. Reproduced from Mannermaa *et al.* [9].

Drug	Mode of Administration	Transporter[a]	References
Antibiotics			
Ampicillin	Topical, intravitreal, subconjunctival	Mouse Npt1, PEPT1, rat Pept2	[95, 166, 167]
Carbenicillin	Topical, intravitreal, subconjunctival	Rat Oat1, rabbit OAT	[168, 169]
Cefazolin	Topical, intravitreal, subconjunctival	OAT1, OAT2, OAT3, OAT4	[170, 171]
Ceftazidime	Intravitreal, subconjunctival	Rat Oat1	[168]
Penicillin G	Topical, subconjunctival	OAT1, OAT3, OAT4, OATP1B1, OATP1B3, rat Oatp1a1, rat Oat1a3_v2, NPT1, PEPT1	[172-181]
Ciprofloxacin	Topical, intravitreal	BCRP, rabbit MCT, mouse MRP-like transporter, rat Oct1	[115, 182-186]
Norfloxacin	Topical	BCRP	[185]
Levofloxacin	Topical	Mouse MRP-like transporter, OCT2-A, rat Oatp1a3_v2, P-gp	[178, 183, 184, 187, 188]
Ofloxacin	Topical	BCRP, rabbit MCT, MRP1, rat Oct, rat P-gp	[115, 185, 189-191]
Erythromycin	Topical, intravitreal, subconjunctival	MRP1, OAT2, OATP1A2, rat Oatp1a4, rat Oatp1b2, P-gp	[189, 192-195]
Tetracycline	Topical	OAT1, OAT2, OAT3, OAT4	[196]
Fusidate	Topical	Rat Bsep, rat Mrp2	[197]
Antifungal agents			
Clotrimazole	Topical	MRP1	[198]
Miconazole	Topical, intravitreal, subconjunctival	P-gp	[199]
Anti-viral drugs			
Acyclovir	Topical	OAT1, rat Oat1, OCT1	[200, 201]
Cidofovir	Intravitreal, systemic	OAT1, rat Oat1	[202, 203]
Foscarnet	Intravitreal, systemic	Rat Mct1, mouse Npt1	[167, 204]
Ganciclovir	Intravitreal, systemic	MRP4, OAT1, OCT1	[201, 205]
Idoxuridine	Topical	Rat Cnt1, rabbit CNT3	[206, 207]
Trifluridine	Topical	Rat Oat1	[200]
Valacyclovir	Systemic	Mouse $ATB^{0,+}$, OAT3, human PEPT1, rat Pept2	[201, 208-210]
Zidovudine (AZT)	Systemic	BCRP, rat Cnt1, MRP4, OAT1, rat Oat1, OAT2, OAT3, OAT4, rat Oat1p1a3_v1, rat Oatp1a3_v2	[200, 201, 211-215]
Anti-inflammatory agents			
Dexamethasone	Topical, intravitreal, subconjunctival	BCRP, OATP1A2, rat Oatp1a1, rat Oatp1a3_v2, P-gp	[177, 216-221]
Hydrocortisone	Topical	Rat Oatp1a1, P-gp	[222, 223]
Methylprednisolone	Subconjunctival	P-gp	[218]
Prednisolone	Topical	$OATP1B3^{b}$, rat Oatp1a1, rat Oatp1a3_v2, P-gp	[178, 181, 218, 221]
Triamcinolone	Intravitreal	$BCRP^{c}$	[216, 217]
Nonsteroidal anti-inflammatory drugs (NSAIDs)			
Diclofenac	Topical	OAT1, OAT2, OAT3, OAT4, OCT1, rat Oat2, rabbit MCT	[115, 174, 215, 224]
Flurbiprofen	Topical	Rabbit MCT, OAT1	[115, 225]
Antifibrotic agents			
5-Fluorouracil	Topical, intravitreal, subconjunctival	MRP5, MRP8	[226, 227]

Cont'd.

Table 2 Cont'd.

Drug	Mode of Administration	Transporter[a]	References
Antiglaucoma drugs			
Carbachol	Topical	Rabbit OCT	[47]
Brimonidine	Topical	OCT	[47, 228]
Dipivefrine	Topical	Rabbit OCT	[47]
Timolol	Topical	OCT, P-gp	[229, 230]
Unosprostone carboxylate[d]	Topical	OATP1A2, OATP2B1, OATP4A1	[231]
H1 receptor antagonists			
Azelastine	Topical	P-gp	[232]
Ketotifen	Topical	P-gp	[233]
Immunomodulators			
Cyclosporine	Topical	BCRP, MRP1, MRP2, OATP1B1, OATP1B3, OATP2B1m rat Oatp1a1, rat Oatp1a4, P-gp	[180, 181, 234-237]
Diagnostic agents			
Fluorescein	Topical, intravenous	MCT, MRP1, OAT1, mouse Oat3	[238-243]

Systemic: oral (PO) or intravenous (IV)
[a]Capital letters; human transporter
[b]Prednisolone phosphate
[c]Contradictory findings
[d]De-esterified form

[34]. The peptide transporters PEPT1 and PEPT2 have been detected on clonetics human corneal epithelium (cHCE) and on human cornea [121, 131]. Furthermore, PepT-2 mRNA has been reported on retinal Muller cells [103] and also on retina when vitreous clearance of cephalosporins were studied using ocular microdialysis [104]. Various drugs have been reported to be substrates of these transporters; for instance, β-lactam antibiotics, and renin- and ACE-inhibitors are substrates for PepT1 and PepT2 [34]. More studies to correlate protein expression and localization of peptide transporters to transport activity are necessary to better understand their relevance to ocular drug delivery. Nevertheless, monocarboxylate (SLC16), organic cation/anion (SLC22), nucleoside (SLC28 and SLC29), and vitamin transporters have been reported in various ocular tissues [12, 61, 132-134]. Atluri *et al.* demonstrated the role of an oligopeptide transporter in glycosarcosine ocular bioavailability. The transporter inhibitors decreased the ocular bioavailability of glycosarcosine [106].

As described above there are various transporters that have been identified in ocular cell lines and tissues. Therefore, various approaches have been pursued to circumvent efflux transporters or to take advantage of the influx transporters. The most common approach is using transporter-targeted prodrugs (Table 3) [12]. This approach has led to improvements in ocular bioavailability of various drugs since it takes advantage of the ocular influx transporters or due to changes in physicochemical properties in the prodrugs or by a combination of these two factors. In general, the prodrugs are recognized by the ocular membrane transporters as substrates and allow their translocation across the epithelia. So far this approach has been undertaken for transporter-targeted drug delivery to cornea, conjunctiva and RPE [12]. For instance, studies on acyclovir and acyclovir prodrugs demonstrated not only that peptide transporters like PepT1 are present on the corneal epithelium, but also play an active role in the transport of these prodrugs. The presence of a facilitative transporter, OATP2A1, was demonstrated in cornea, conjunctiva, iris and ciliary body and its role in the permeability of both latanoprost and its free acid metabolite was reported [87]. More examples are presented in the section below.

Table 3. Transported-Targeted Prodrugs for Ocular Drug Delivery (modified from Gaudana *et al.* [12] with permission).

Transporter System-targeted Tissue/cell Line	Drug/prodrug Employed	Observation	Reference
$B^{0,+}$ on the cornea	L-asparate ACV	Four-fold higher transcorneal permeability of L-aspartate ACV compared to ACV	[244]
$B^{0,+}$ on the cornea	Gamma-glutamate-ACV (EACV)	Higher aqueous solubility of the prodrug along with the transporter recognition	[245]
$B^{0,+}$ on the cornea	Phenylalanine-ACV and EACV	The prodrugs inhibited the transport of L-arginine[a] across the cornea implied that they are substrates of $B^{0,+}$	[126]
OPT system on the cornea	L-valine ACV	Three-fold higher transcorneal permeability of L-valine ACV compared to ACV	[157]
OPT system on the cornea	Gly-Val-GCV, Val-Val-GCV and Tyr-Val-GCV	Significant transcellular passive diffusion and transporter recognition resulted in higher AUC and C_{max}	[246, 247]
OPT system on rPCEC cells and the cornea	Val-quinidine and Val-Val-quinidine	Prodrugs were not recognized by P-gp efflux pump and further found to be substrates of peptide transporters	[248]
OPT system on the retina	Gly-Val-GCV, Val-Val-GCV and Tyr-Val-GCV	Two-fold higher RCS tissue permeability than that of GCV due to higher lipophilicity and translocation mediated by OPT across RPE	[249]
SMVT on the retina	Biotin-GCV	Higher biotin-GCV permeability into the retina-choroid and slower elimination from vitreous	[250]
GLUT1 on the HRPE cells	Glu-dopamine	Transporter recognizes prodrug, not the parent drug	[251]

OPT oligopeptide transporter, SMVT sodium-dependent multiple vitamin transporter, $B^{0,+}$ amino acid transporter, GLUT glucose transporter, rPCEC rabbit primary corneal epithelial cells, HRPE human retinal pigment epithelium cells, RCS retina-choroid-sclera, ACV acyclovir, GCV ganciclovir, RPE retinal pigment epithelium
[a]Substrate of $B^{0,+}$

FORMULATION DEVELOPMENT INCLUDING PRO-DRUG APPROACH EFFECTING TRANSPORTERS

A majority of ocular diseases are treated using topical ocular administration. A major drawback of this route has been the poor residence time which leads to very little drug absorption into the intraocular tissues. Viscosifying agents like tamarind gum, HPMC, cremophor, CMC, xanthan gum, etc., have been investigated and reported to increase drug residence time on the surface of the eye [135-143]. Some surface active agents like benzalkonium chloride and EDTA have been investigated for their penetration enhancing ability [80, 81, 83, 144-146]. The intent of this section is to review any formulation approaches that affect transporters to enhance ocular drug exposures and bioavailability.

Formulation approaches have been used in oral and systemic drug delivery to modify transporter function and improve systemic bioavailability. A good example is Vitamin E-TPGS which has been used in conjunction with amprenavir as an excipient to inhibit P-gp and improve the oral bioavailability of amprenavir [147]; a study with paclitaxel also demonstrated similar results [148]. Other commonly used excipients like cyclodextrins, Labrasol™, cremophor, polyethylene glycols (PEGs) and pluronics have also been shown to inhibit transporters [149-156]. While these approaches seem to be common in oral drug delivery, such an investigation is lacking in the field of ophthalmic drug delivery. Some of the above mentioned excipients like xanthan gum, EDTA, cremophor and PEGs, which are used in eye drops for topical ocular delivery have been shown to inhibit transporters and can potentially play a role in increasing ocular tissue exposures. However, studies to determine the contribution of transporter inhibition and increased residence time/penetration enhancement have not been done. Investigations into approaches to avoid transporters would be

useful to improve ocular drug bioavailability.

Prodrugs which are metabolized to the active moiety *in vivo* have been used in ocular drug delivery (Table 2). Latanoprost, when administered via topical ocular route is metabolized *in vivo* to its active form. It was demonstrated that OATP2A1, which is expressed in both RPE/choroid and anterior segment tissues like cornea, conjunctiva, iris and ciliary body, plays a role in the permeability of both latanoprost and its free acid metabolite [87]. In another study, it was demonstrated that bimatoprost and latanoprost and their free acid metabolites were substrates of MRP1, MRP2 and MRP5, using MDCK cell lines over-expressing these transporters and excised rabbit cornea [82]. Furthermore, it has been reported that acyclovir prodrugs, which utilize both ocular transporter and enzyme interplay can be used to deliver drugs to the eye [157-159].

CURRENT AND FUTURE RELEVANCE OF OCULAR TRANSPORTERS IN DRUG DEVELOPMENT

Many clinically available ophthalmic drugs are known to be either substrates or inhibitors of transporters, and are presented in this review. While the expression and presence of both facilitative and efflux transporters has been demonstrated, knowledge of their role in affecting ocular pharmacokinetics in preclinical species is limited. Their relevance to clinical ocular pharmacokinetics has not been demonstrated.

A drug-drug interaction between oral/systemically administered compounds and topical ocular administered compounds can occur where either of the molecules can be a victim or perpetrator of the interaction. Oral and systemically administered drugs can distribute to the eye due to the action of transporters. These molecules can interact with topically administered drugs altering their local ocular pharmacokinetics, safety and efficacy. In the same way, topically administered molecules can affect the ocular distribution of orally administered compounds by inhibiting the efflux transporters in blood-ocular barriers, of which the oral/systemically administered compounds are substrates. Hippalgoankar *et al.* in fact showed that such drug-drug interactions are possible by studying the interaction between a topically administered and systemically administered P-gp substrates/inhibitors [74]. Thus, these transporters play an important role in affecting the ocular disposition of the drugs and affect their therapeutic action of the drugs. At the same time such oral and systemically administered drugs distributing to the eye due to transporter mediated drug-drug interactions can cause unwanted ocular effects.

Interplay between enzymes and transporters, like CYP3A4 and P-gp has been well studied [160-165]. However, the same cannot be said of ophthalmic drug delivery. Some of the prodrug approaches used in ocular drug delivery, which utilize the interplay of enzymes and transporters, are mentioned in this review. These studies demonstrate that ocular tissue levels of the active metabolite can be modified by the action of the efflux and facilitative transporters. Such studies demonstrate that enzyme transporter interplay is possible in ocular drug delivery and needs to be further investigated, either to the advantage of drug development and delivery or to prevent possible pitfalls which can arise due to genetic differences in the populations of transporters and enzymes.

Molecules which are designed to utilize body's existing transporter systems to improve their systemic and target organ/tissue bioavailability can be used to improve posterior segment drug exposures upon topical ocular delivery as also for decreasing systemic drug exposures upon intraocular (intravitreal or intracameral) administration. Such approaches are currently being tested in the clinic with oral drug delivery.

CONCLUSIONS

While the expression and presence of transporters in the eye has been well demonstrated, studies to understand their role in ocular drug delivery, vis-à-vis their role in ocular pharmacokinetics, efficacy and safety, are only in their infancy. While the role of transporters in ocular homeostasis is known, a disruption of these mechanisms by drugs modifying transporter function needs to be studied. While the *in vitro* and *in vivo* techniques for investigating the role of transporters in ocular drug delivery already exist, intensive investigation needs to be carried out before their clinical relevance can be elucidated and understood.

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